Monitor: molecules and profiles

Monitor provides an insight into the latest developments in drug discovery through brief synopses of recent presentations and publications together with expert commentaries on the latest technologies. There are two sections: *Molecules* summarizes the chemistry and the pharmacological significance and biological relevance of new molecules reported in the literature and on the conference scene; *Profiles* offers commentary on promising lines of research, emerging molecular targets, novel technology, advances in synthetic and separation techniques and legislative issues.

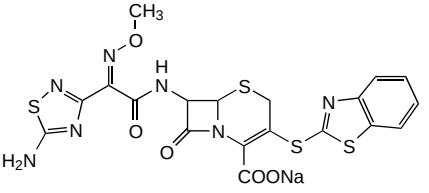
Anti-MRSA agents

The increasing incidence of antibiotic-resistant bacterial infections in hospitals, particularly nosocomial and opportunistic infections caused by multiple drug-resistant Gram-positive bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA), are of major concern to the various national health authorities. This has led to an increase in research activity in this field and the re-evaluation of various classes of antibiotics to identify potential lead candidates for development in this battle against microbial pathogenesis.

Cephalosporin derivatives

Although various cephalosporin derivatives have been shown to have high potency and broad-spectrum antibacterial activity against Gram-negative bacteria such as *Pseudomonas aeruginosa*, there low-activity against Gram-positive organisms generally limits their clinical use. Tsushima, M. and coworkers have described the synthesis of a series of novel cephalosporin derivatives with various bicyclic heterocycles at the C-3 position [*Bioorg. Med. Chem.* (1998) 6, 1009–1017].

Compound **1** (CP0467) was shown to possess exceptional activity against MRSA (MIC_{90} = 6.25 μg ml^{-1}) and high affinity for the penicillin-binding protein PBP-2' of MRSA (IC_{50} = 0.48 μg ml^{-1}). Pharmacokinetic studies in four-week old Jcl:ICR mice also showed that **1** has a long-acting pharmacokinetic profile (AUC_{∞} = 482.3 μg h^{-1} ml^{-1}; $t_{1/2}$ = 1.9 h).

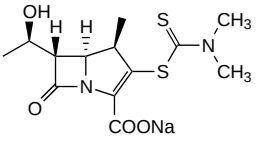


1

Novel dithiocarbamate carbapenems

Another recent paper from a group at Tsukuba Research Institute, Banyu Pharmaceutical Co. (Tsukuba, Japan) has reported the anti-MRSA activity of a novel series of 1β-methyl carbapenems in which the C-2 position of the carbapenem has been modified with disubstituted-aminothiocarbonylthio moieties [Ohtaka, N. *et al. Bioorg. Med. Chem.* (1998) 6, 1089–1101].

These compounds were found to have high affinity for the PBP-2' binding protein of MRSA and good *in vitro* antibacterial activity against high-level MRSA. Selected compounds, including **2** (MIC = 3.13 μg ml^{-1}; IC_{50} = 9.6 μg ml^{-1}) were evaluated *in vivo*. The majority of these compounds showed anti-MRSA activity comparable with, or superior to, vancomycin. Compound **2** had one of the best pharmacokinetic profiles (AUC_{∞} = 1061 μg h^{-1} ml^{-1}; $t_{1/2}$ = 27.6 min).



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Growth hormone secretagogue

Growth hormone has important roles in the promotion of growth and enhancement of anabolic processes. Although recombinant human growth hormone (rGH) has been successfully used in the treatment of children with growth-hormone deficiency and in reversing the effects of ageing in the elderly, there are various side effects that may be attributed to the subcutaneous bolus administration of rGH. The recent identification of compounds that stimulate the pituitary gland to release growth hormone in a pulsatile pattern has encouraged various groups to seek small-molecule mimetics.

A group from Merck Research Laboratories (Rahway, NJ, USA) have recently reported the identification of 1-[2(*R*)-(2-amino-2-methylpropionylamino)-3-(1*H*-indol-3-yl)propionyl]-3-

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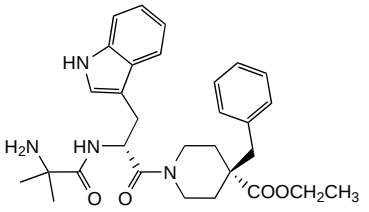
benzylpiperidine-3(*S*)-carboxylic acid ethyl ester (L163540, **3**) as a potent, orally bioavailable, short-acting growth hormone secretagogue [Yang, L. *et al. J. Med. Chem.* (1998) 41, 2439–2441]. This compound was found to be active when administered intravenously to rats (25 ng kg^{-1}) and beagles (5 ng kg^{-1}). On oral administration, bioavailability was found to be 12.1% and 29% in rats and beagles, respectively. The compound will be a useful tool for future long-term efficacy studies.



3

Arginine vasopressin antagonists

The pituitary gland is also responsible for the release of the hormone arginine vasopressin, which exerts its effect via three receptor subtypes – V_{1a}, V_{1b} and V_2 receptors – in response to increased plasma osmolality or decreased blood volume or pressure. The V_2 receptors are located in the kidney where they appear to have a role in the regulation of renal water reabsorption. Antagonists of the V_2 receptor may therefore be useful in the treatment of oedematous states associated with diseases such as congestive heart failure, liver cirrhosis and lung disease. Albright, J.D. and coworkers have reported the identification of 5-fluoro-2-methyl-*N*-[4-(5*H*-pyrrolo[2,1-*c*]-[1,4]benzodiazepin-10(11*H*)-ylcarbonyl)-3-chlorophenyl]benzamide (VPA985, **4**) as an orally active arginine vasopressin antagonist with selectivity

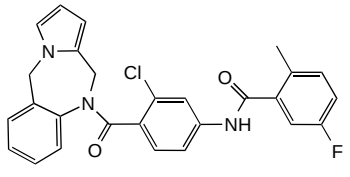


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Table 1. Bioactivity of compounds 5 and 6 against various human tumor cell lines

Human cell line	ED_{50} (μg ml^{-1})		
	5	**6**	**Adriamycin**
A-549	2.8×10^{-6}	1.6×10^{-6}	0.015
MCF-7	4.2×10^{-6}	1.8×10^{-3}	0.250
HT-29	5.7×10^{-6}	1.9×10^{-2}	0.040
A-498	1.00	1.40	0.042
PC-3	1.10	1.20	0.028
PACA-2	1.80	0.28	0.013

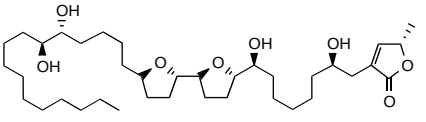
for the V_2 receptor [*J. Med. Chem.* (1998) 41, 2442–2444].

The compound was evaluated in a randomized, double-blind, placebo-controlled, ascending single-dose study in humans. An increase in urine flow and serum sodium concentrations and a dose-dependent decrease in urinary osmolality was observed on administration of 30, 60 and 150 mg doses of **4**.

Natural products

Glabracins A and B

Workers from Purdue University (West Lafayette, IN, USA) and the Walker Cancer Research Institute (Tallahassee, FL, USA) have reported the isolation, characterization and biological evaluation of two new bioactive bis-THF acetogenins, glabracins A (**5**) and B (**6**), from the leaves of *Annona glabra* by activity-directed fractionation using the brine shrimp lethality test [Liu, X-X. *et al. Bioorg. Med. Chem.* (1998) 6, 959–965].



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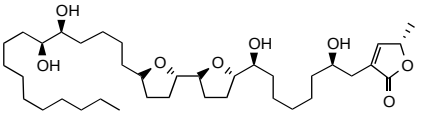

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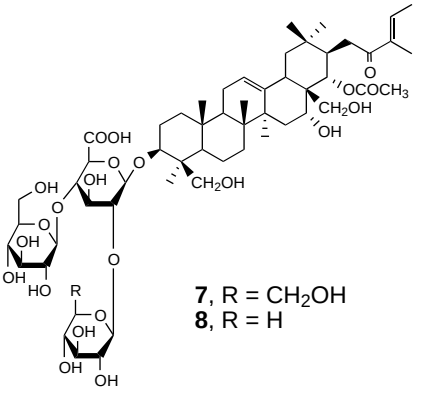
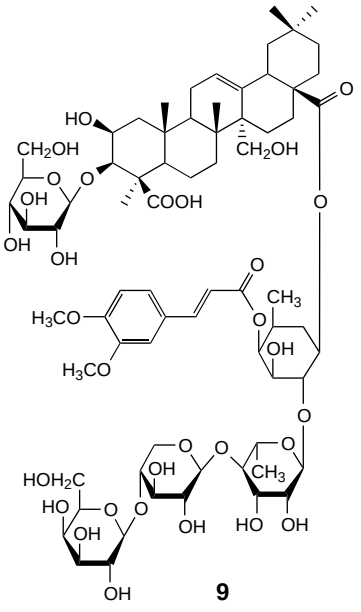
Both compounds **5** and **6** were shown to be cytotoxic to certain human tumour cell lines (Table 1). Although these compounds differ only in the stereochemistry of their vicinal diaols at C-23/24, **5** was more active than **6**. Both compounds were also found to be more selective than adriamycin for particular tumor cell lines.

Glucose uptake inhibitors

Although various traditional Chinese and Japanese medicines are known to have prophylactic and therapeutic effects in the treatment of diabetes mellitus, few active agents have yet to be fully elucidated. As part of their work in this field, a group from Kyoto Pharmaceutical University (Kyoto, Japan) have described an investigation into the mechanism by which the saponins Escins Ia (**7**) and IIa (**8**) and



E,Z-senegin II (**9**), isolated from the seeds of *Aesculus hippocastanum* and *Polygala senega* var. *latifoloa*, inhibit elevation of serum glucose in oral glucose-loaded rats [Matsuda, H. *et al. Bioorg. Med. Chem.* (1998) 6, 1019–1023].



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Although these compounds were shown to inhibit serum glucose level increase in oral glucose-loaded rats, they had no effect on serum glucose levels in either normal rats, intraperitoneal glucose-loaded rats or alloxan-induced diabetic mice. However, the compounds were shown to inhibit gastric emptying in rats and to inhibit glucose uptake across rat small intestine *in vitro*. These compounds, therefore, appear to act by slowing the gastric transit from the stomach to the small intestine and by inhibiting glucose uptake by the intestinal epithelia.

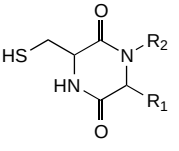
Combinatorial chemistry

Matrix metalloproteinase inhibitors

Many inhibitors of the matrix metalloproteinases (MMPs) have been previously reported, several types being produced in combinatorial libraries. A recent paper describes the design of MMP inhibitors based on diketopiperazines (DKPs) [Szardenings, A.K. *et al. J. Med. Chem.* (1998) 41, 2194–2200]. The synthesis of DKPs on solid-phase has been reported many times, but in the library described, the compounds contain a thiol group designed to chelate the catalytic metal ion.

Two libraries of 684 compounds were prepared in 36 pools of 19 compounds on TentaGel resin and tested against collagenase-1, gelatinase-B, stromelysin-1 and matrilysin. The second of these libraries (**1**) contained either L- or D-cysteine to provide the zinc-chelating group, and varied R_1 (from 19 amino acid precursors) and R_2 (from 18 aldehyde precursors) as potential side chains to S1' and S2' subsites, respectively.

Screening the compound mixtures, and deconvolution of the most active mixtures confirmed that the S1' pocket is the primary specificity determining site, whereas the group that occupied S2' could be varied while maintaining inhibitory activity. Deconvolution of the anisaldehyde-derived mixture revealed that cyclohexylalanine was the preferred residue in R_1 for activity against collagenase-1 and gelatinase-B (**2**).



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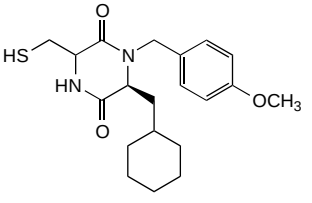

2

Substrate-based protein tyrosine kinase inhibitors

Protein tyrosine kinases (PTKs) are enzymes that phosphorylate specific tyrosine residues in a wide variety of functional proteins and have a role in regulating numerous cellular processes. One key role of PTKs is in the process of tumourogenesis, and this has suggested the potential for inhibitors as antiproliferative drugs.

One bead-one-peptide combinatorial libraries have been previously used to determine the heptapeptide substrate sequence, YIYGSFK-NH_2, for the p60c-src PTK [Lam, K.S. *et al. Int. J. Pept. Protein Res.* (1995) 45, 587–592]. A new paper describes the design and synthesis of inhibitors of this PTK, based on the substrate sequence [Alfaro-Lopez, J. *et al. J. Med. Chem.* (1998) 41, 2252–2260]. Over 70 analogues were prepared with a focus on conformational and topographical constraints, especially through the generation of a cyclic β-turn mimic using an intramolecular disulphide bond. The two most potent structures contained two new nonphosphorylatable tyrosine mimetics giving IC_{50} values of 0.13 and 0.54 μM. These compounds were 420- and 100-fold more active, respectively, than the starting peptide in this study, although they showed poor Lck/Src selectivity. Co-crystallization studies may generate more information about the binding modes of these compounds that may lead to the design of superior inhibitors.

Solid-phase carbohydrate synthesis

Carbohydrates are important mediators of cellular recognition and adhesion, and the initial events in viral and bacterial infections. Consequently, oligosaccharides provide important targets for drug discovery through combinatorial synthesis. However, until very recently there were very few effective ways of making these molecules in an efficient and stereocontrolled fashion. Last year, Nicolaou's group described a reiterative solid-phase approach that depended on the use of thioglycosides as the glycosyl donors [Nicolaou, K.C. *et al. J. Am. Chem. Soc.* (1997) 119, 449–550]. Unfortunately, this methodology was limited by the generation of mixtures of anomers at each cleavage stage and the need to reactivate cleavage fragments before they could be reincorporated into the growing oligosaccharide.

A recent paper from the same group describes modifications to the chemistry that overcome both of these problems [Nicolaou, K.C. *et al. Angew. Chem., Int. Ed. Engl.* (1998) 37, 1559–1561]. The oligosaccharides were

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