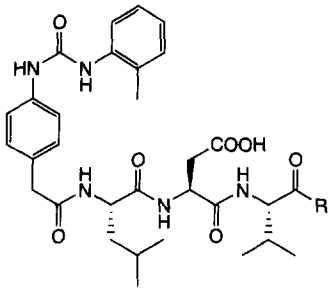
# Monitor: molecules and profiles

*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.

## $\alpha_4\beta_1$ Integrin inhibitors

The $\alpha_4\beta_1$ integrin (often referred to as VLA-4) is expressed on all mononuclear leukocytes and binds to the cytokine-inducible endothelial cell surface-protein vascular cell-adhesion molecule-1 (VCAM-1). Inhibitors of this integrin have potential therapeutic application in a wide range of inflammatory and autoimmune diseases.

A recent interesting review from C.N. Zimmerman describes the discovery of all the various peptide, peptidomimetic and small-molecule inhibitors of VLA-4 that have been published in the patent literature [*Exp. Opin. Ther. Patents* (1999) 9, 129–133]. The most promising of these compounds (**1**, **2**), developed by Biogen (Cambridge, MA, USA), have subnanomolar $IC_{50}$s and have been shown to potently inhibit late-phase bronchoconstriction, as well as airway hyperresponse, in the allergic sheep airway-hyperresponse model [WO9703094]. Some of these inhibitors are now in clinical trials; the data should provide an indication of whether VLA-4 inhibitors are useful as anti-inflammatory therapeutics.



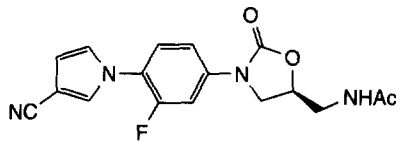
**1**, R = OH
**2**, R = Proline

## Novel antibacterial agents

The increasing emergence of multi-drug resistant strains of Gram-positive bacteria has led to a need to identify novel antibiotics that are not cross-resistant with other agents.

The oxazolidinones are one such class of totally synthetic agents that have potent activity against Gram-positive organisms. These agents act by selectively binding to the bacterial 50S ribosomal subunit thereby inhibiting bacterial translation at the early stage of protein synthesis.

A recent communication from workers at Pharmacia & Upjohn (Kalamazoo, MI, USA) has described the synthesis and evaluation of a range of pyrrolylphenyl- and pyrazolylphenyl-oxazolidinones as broad-spectrum antibiotics [Genin, M.J. *et al.* (1998) *J. Med. Chem.* 41, 5144–5147]. In particular, compounds PNU171933 (**3**) and PNU172576 (**4**) were found to have very potent activity against both Gram-positive and Gram-negative organisms, with *Staphylococcus aureus* MICs $\leq 0.5$ μg ml$^{-1}$ and *Haemophilus influenzae* and *Moraxella catarrhalis* MICs = 2–4 μg ml$^{-1}$.



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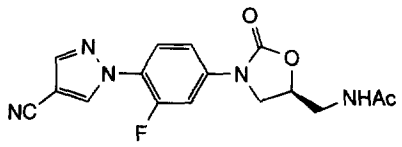

**4**

Both compounds also showed excellent pharmacokinetic profiles and were shown to be more effective than earlier generation compounds against *S. aureus* and *Streptococcus pneumoniae* in mouse models of human infection.

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