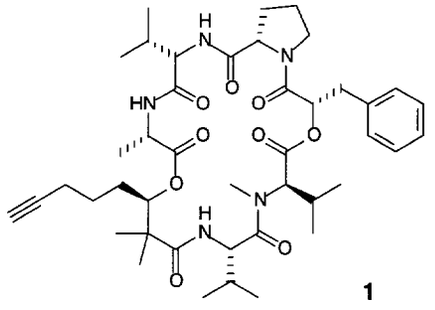
Monitor: molecules and profiles

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.

Cytotoxic natural products

Reese, M.T. and coworkers [*J. Am. Chem. Soc.* (1996) 118, 11081–11084] have described the isolation of a cyclic depsipeptide, kulolide (**1**), from a cephalaspidean mollusc, *Philinopsis speciosa*. This compound was shown to be active against L-1210 leukaemia cells (IC_{50} = 0.7 μg/ml) and P388 murine leukaemia cells (IC_{50} = 2.1 μg/ml) but showed no toxicity against brine shrimp at 1.0 ppm. Morphological changes resulting in the formation of protuberances from the cell surface, typical of actin-polymerization inhibitor activity, were observed on treatment of rat 3Y1 fibroblasts with **1** at 50 μM, suggesting that this compound may act as an actin-depolarization agent.



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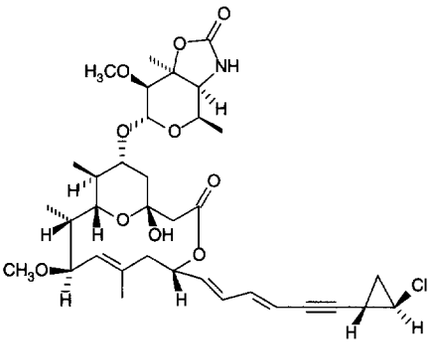
Another group [Zampella, A. *et al. J. Am. Chem. Soc.* (1996) 118, 11085–11088] has described the isolation of a cytotoxic glycoside macrolide, callipeltoside A (**2**), from the marine lithisid sponge *Callipelta sp.* Akin to several other marine-derived macrolides this compound was found to have cytotoxic activity against NSCLC-N6 human bronchopulmonary non-small-cell lung carcinoma (IC_{50} = 11.26 μg/ml) and P388 murine leukaemia (IC_{50} = 15.26 μg/ml). Flow cytometry of NSCLC-N6 cells demonstrated that callipeltoside A exerts a cell cycle G_1-dependent effect indicative of inhibition of cell proliferation at G_1 by enzymes or by induction of terminal cell differentiation. The authors suggest that in the latter case callipeltoside A would be an interesting mechanism-based lead and are therefore presently undertaking further biological evaluation of this compound.



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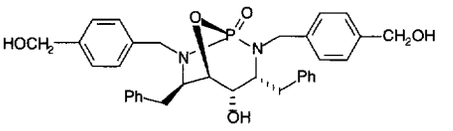
Bicyclic HIV protease inhibitors

Recent clinical studies have suggested that HIV protease inhibitors used alone or in combination with retroviral transcriptase inhibitors have therapeutic utility



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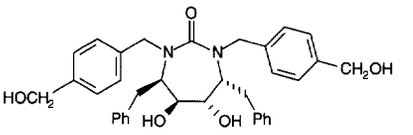

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in the treatment of HIV. Smallheer, J.M. and Seitz, S.P. [*Heterocycles* (1996) 43, 2367–2376] report the synthesis and evaluation of a series of (3-*endo*,4-*endo*, 6-*exo*)-8-oxa-7-diaza-1-phosphabicyclo-[3.2.1]octanols as inhibitors of HIV protease. Of these bicyclic compounds, compound **3** (K_i = 0.6 nM; IC_{90} = 154 nM) was found to have a similar activity profile to the cyclic urea HIV protease inhibitor DMP323 (**4**), which is already in clinical trials. This compound contains a hitherto unreported heterocyclic system and provides an alternative structural scaffold from which to develop future HIV protease inhibitors.

CCK_B antagonists

Recent studies suggest that cholecystokinin B (CCK_B) antagonists may have application in the treatment of CNS disorders such as anxiety and panic attacks.

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