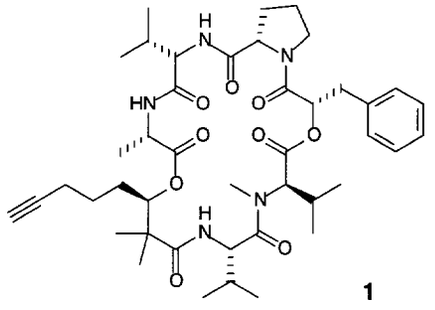
Monitor: molecules and profiles

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.

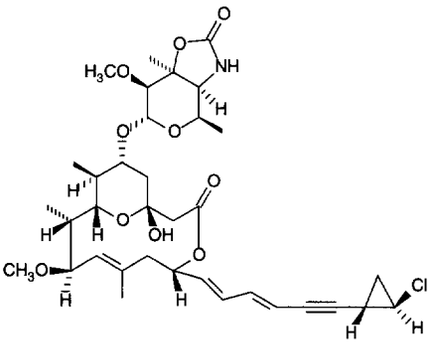
Cytotoxic natural products

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.



1

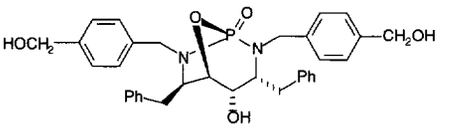
Another group [Zampella, A. *et al. J. Am. Chem. Soc.* (1996) 118, 11085–11088] has described the isolation of a cytotoxic glycoside macrolide, callipeltoside A (**2**), from the marine lithisid sponge *Callipelta sp.* Akin to several other marine-derived macrolides this compound was found to have cytotoxic 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.



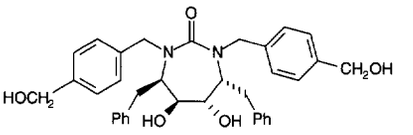
2

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



3



4

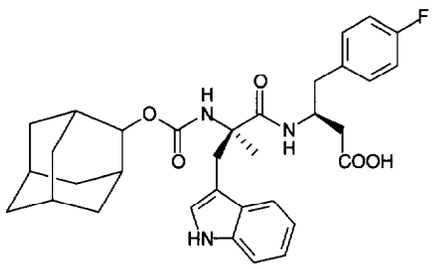
in the treatment of HIV. Smallheer, J.M. and Seitz, S.P. [*Heterocycles* (1996) 43, 2367–2376] report the synthesis and evaluation of a series of (3-*endo*,4-*endo*, 6-*exo*)-8-oxa-7-diaza-1-phosphabicyclo-[3.2.1]octanols as inhibitors of HIV protease. Of these bicyclic compounds, compound **3** (K_i = 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.

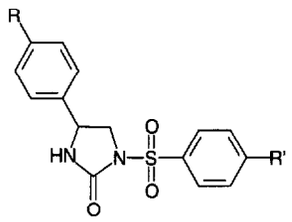
Monitor Editor: **Andrew W. Lloyd**, Department of Pharmacy, University of Brighton, Cockcroft Building, Moulsecoomb, Brighton, UK BN2 4GJ. tel: +44 1273 642049, fax: +44 1273 679333, e-mail: a.w.lloyd@brighton.ac.uk

A recent study [Augelli-Szafran, C.E. *et al. Bioorg. Med. Chem.* (1996) 4, 1733–1745] has identified a 4-fluorophenyl analogue of the known CCK_B receptor antagonist CI988 (**5**) with extraordinary binding affinity for the CCK_B receptor (IC_{50} = 0.08 nM) and 940-fold selectivity for the CCK_B receptor over the CCK_A receptor.

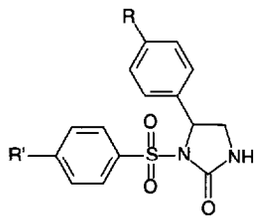


5

Arylsulphonylimidazolidinones as anticancer agents



6

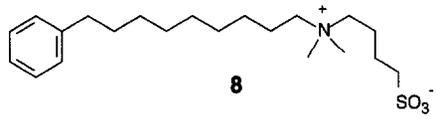


7

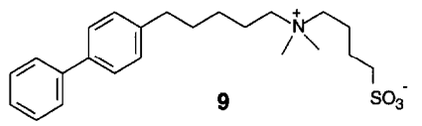
On the basis of recent reports suggesting that diarylsulphonylureas may have therapeutic utility as antineoplastic agents, Jung, S-H. and coworkers [*Bioorg. Med. Chem. Lett.* (1996) 6, 2553–2558] have designed and synthesized two series of novel arylsulphonylimidazolidinones based on **6** and **7** containing the sulphonylurea pharmacophore. These compounds were tested against various human solid tumours, murine leukaemia cell lines *in vitro* and murine mammary adenocarcinoma (MM48) *in vivo*. The results suggest that these novel 1-arylsulphonyl-4-phenylimidazolidinones offer potential as lead compounds for the development of anticancer agents based on the sulphonylurea pharmacophore.

Squalene synthetase inhibitors

Shechter, I. and coworkers [*Bioorg. Med. Chem. Lett.* (1996) 6, 2585–2588] have described an investigation into the use of sulphobetaines as zwitterionic squalene synthetase inhibitors. These compounds presumably mimic both the carbocationic and anionic moieties of the squalene synthetase reaction intermediates while maintaining overall neutrality. The most effective inhibitors identified by this group are those incorporating aromatic hydrophobic chains such as **8** (IC_{50} = 2 μM) and **9** (IC_{50} = 2 μM).



8

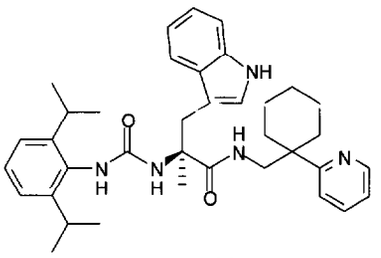


9

Nonpeptide NMB antagonist

Although the neuromedin B (NMB) decapeptide and the structurally related 27-amino-acid gastrin-releasing peptide are thought to mediate a range of biological actions, including autocrine growth, satiety and thermoregulation, the precise physiological role of these peptides has yet to be fully elucidated as a partial consequence of the lack of suitable nonpeptide high-affinity antagonists.

To address this, a group from the Parke-Davis Neuroscience Research Centre (Cambridge, UK) [Eden, J.M. *et al. Bioorg. Med. Chem. Lett.* (1996) 6, 2617–2622] have developed a novel series of nonpeptide NMB antagonists, exemplified by **10** (PD165929), using a 'peptoid' drug design strategy.

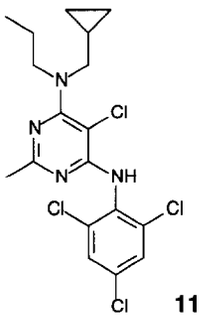


10

PD165929 was shown to be the first high affinity (K_i = 6.3 nM) competitive antagonist ($_{app}K_b$ = 7.6 nM) at the NMB receptor with greater than 1000-fold selectivity for this receptor over the related gastrin-releasing peptide receptor type.

CRF_1 receptor antagonists

The investigation into the role of corticotropin-releasing factor (CRF) in depression, anxiety and stress-related disorders has also been hampered by the lack of suitable nonpeptide antagonists. The actions of CRF are mediated through a family of G-protein-coupled seven-transmembrane protein receptors of which two subtypes, CRF_1 and CRF_2, have been recently cloned, expressed and characterized. Workers from Neurocrine Biosciences (San Diego, CA, USA) have reported the design and synthesis of a series of high affinity, selective, nonpeptide CRF_1 antagonists based on 4-anilino-6-aminopyrimidines such as **11** [Chen, C. *et al. J. Med. Chem.* (1996) 39, 4358–4360]. These compounds were shown to have low nanomolar affinities for the human CRF_1 receptor subtype and shown to inhibit CRF-stimulated cAMP production in stable cell lines transfected with this subtype *in vitro*. These compounds will be particularly useful for establishing the potential use of CRF_1 receptor antagonists in the treatment of depressive and anxiety-related disorders.



11