Monitor: molecules and profiles

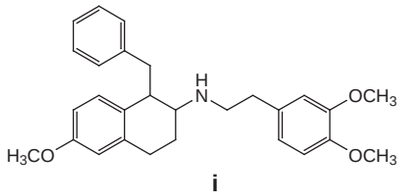
Monitor provides an insight into the latest developments in drug discovery through brief synopses of recent presentations and publications together with expert commentaries on the latest technologies. There are two sections: *Molecules* summarizes the chemistry and the pharmacological significance and 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.

Molecules

Neuropeptide Y Y_5-receptor antagonists

The 36-amino acid, neuropeptide Y, has been found in both the central and peripheral nervous systems, where it acts to stimulate feeding. Two receptor subtypes, Y_1 and Y_5, are responsible for the centrally-mediated neuropeptide Y feeding response. Compounds that act as Y_5-receptor antagonists reduce food intake in animal models. There is therefore an interest in developing novel Y_5-receptor antagonists as potential therapeutic treatments for eating disorders and obesity.

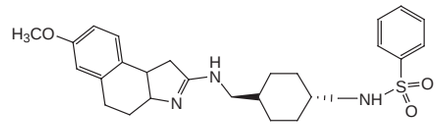
McNally, J.J. and coworkers identified a novel *N*-phenethyl-α-benzyl-β-aminotetralin (**i**) with micromolar binding affinity for the human Y_5 receptor.



i

On the basis of this observation, this group has prepared a series of [3a,4,5,9b-tetrahydro-1*H*-benzo[*e*]indol-2-yl]amines by reductive amination and concomitant cyclization of α-cyanomethyl-β-aminotetralins. These compounds were *N*-acylated with Ω-sulfonamido-carboxylic acids and reduced to yield a series of *N*-(sulfonamido)alkyl[tetrahydro-1*H*-benzo[*e*]indol- 2-yl]amines[1].

The ability of these compounds to bind to the Y_5 receptor was evaluated using HEK293 cells that were stably transfected with human neuropeptide Y_5 cDNA and the competitive inhibition of the binding of the ^{125}I-labelled neuropeptide ligand (PYY) was measured. Compound (**ii**) demonstrated the highest binding affinity (IC_{50} = 1 nM) and



ii

was shown to be an antagonist using an assay that monitored the stimulation of labelled GTPgS binding in a Bowes melanoma cell line transfected with the human Y_5 receptor. This molecular scaffold might provide a useful pharmacophore for the future development of other Y_5 ligands.

1 MaNally, J.J. *et al.* (2000) *N*-(sulfonamido)alkyl[tetrahydro-1*H*-benzo[*e*]indol-2-yl]amines: Potent antagonists of human neuropeptide Y Y_5 receptor. *Bioorg. Med. Chem. Lett.* 10, 213–216

Potent cRAF1 kinase inhibitors

The formation of many human tumours occurs as a consequence of mutation, overexpression and receptor-mediated hyperactivation of *ras* genes. The protein kinase cRAF1 plays a major role in RAS signal transduction as it is the first enzyme in the mitogen-activated protein (MAP) kinase cascade. cRAF1 has also been reported to downregulate apoptosis, the programmed cell death process that serves to prevent proliferation of cancer cells. Inhibition of this enzyme might therefore offer an effective strategy for anticancer therapy.

Lackey, K. and coworkers have recently reported the synthesis and evaluation of a series of benzylidene-1*H*-indol-2-one (oxindole) derivatives as potential cRAF-1 kinase inhibitors[2]. The group screened over 2000 compounds in the benzylidene oxindole series using a two-step approach involving an initial cascade assay of three non-homologous kinases consisting of RAF,

Monitor Editor: **Andrew W. Lloyd**, School of Pharmacy and Biomolecular Sciences, 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

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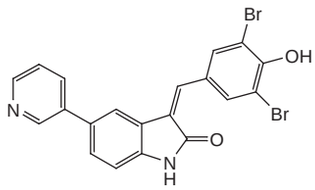
MEK (MAP kinase/ERK kinase), ERK2 (extracellular-regulated kinase) and the subsequent target identification of the potent cascade inhibitors.

As inhibition of cRAF1 kinase should cause down-regulation of MAP kinase activity, the group also used a cell-based mechanistic assay to measure the inhibition of endothelial growth factor-stimulated MAP kinase activation. This study identified several potent cRAF1 kinase inhibitors, exemplified by (**iii**), demonstrating low nanomolar kinase enzyme inhibition that also inhibited the MAP kinase pathway *in vitro*.



iii

2 Lackey, K. *et al.* (2000) The discovery of potent cRaf1 kinase inhibitors. *Bioorg. Med. Chem. Lett.* 10, 223–226

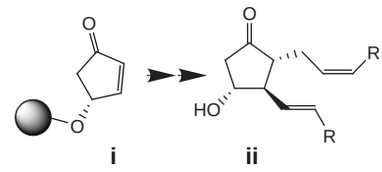
Andrew Lloyd

Combinatorial chemistry

Antiviral prostanoid libraries

The prostaglandin family constitutes one of the most pharmacologically active low-MW chemical classes in existence. A library of prostanoid analogues has been prepared on a soluble polymer support and used to find novel inhibitors of a herpes family virus[1].

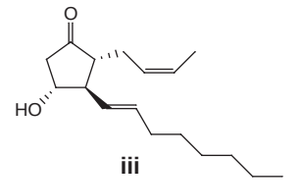
A 'parallel pool' library strategy was employed in which small pools of compounds were modified through several different functionalization reactions. Starting with the enone (**i**) attached to a soluble polystyrene support, several different ω- and α-chains were added to generate the library (**ii**). Cleavage of the products from the support using fluoride ions enabled biological evaluation of the library pools, and deconvolution



i **ii**

of active pools gave the identity of the active single analogues.

The library of prostanoids was screened for their ability to inhibit the replication of murine cytomegalovirus (CMV), and the analogue (**iii**) was discovered as the most potent compound.



iii

Although this compound is one order of magnitude less potent than ganciclovir (the most frequently used anti-CMV agent) this level of activity has encouraged the preparation of other structurally related prostanoids in a second generation library to further the search for more active agents.

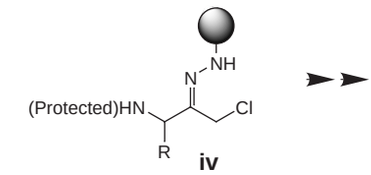
1 Lee, K.J. *et al.* (1999) Soluble-polymer supported synthesis of a prostanoid library: identification of antiviral activity. *Org. Lett.* 1, 1859–1862

Cysteine protease libraries

Cysteine proteases are characterized by the presence of a key nucleophilic cysteine residue in the active site of the enzyme that attacks the carbonyl of the hydrolyzed substrate amide bond. Various cysteine proteases are known to have physiological functions that make them suitable as targets for pharmacological intervention. Examples include calpains (implicated in neurodegeneration), cathepsin K (linked to osteoporosis) and caspases (which are possibly involved in apoptosis).

Various mechanism-based inhibitors have been designed, many of which depend on an electrophilic group such as a carbonyl or Michael acceptor that can react to form a covalent link to the nucleophilic thiol group of the crucial cysteine. A recent publication describes a versatile method of producing ketone-based cysteine protease inhibitors that permits maximal variation of the ketone structure[2].

A chloromethyl ketone, readily prepared from N-protected amino acids, was linked to the solid support by reaction with a hydrazine linker. The tethered carbazate (**iv**) was then derivatized by nucleophilic displacement of the chloride, and further derivitization of



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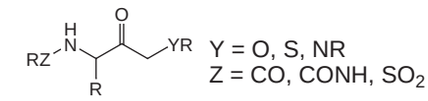

v

the deprotected amine. Several products (**v**) were made, without racemization of the α-chiral centre, and they were ultimately liberated from the solid support with overall yields of 40–100%. Library preparation using this methodology is currently ongoing and the products will be evaluated against representative cysteine proteases.

2 Lee, A. *et al.* (1999) General solid-phase method for the preparation of mechanism-based cysteine protease inhibitors. *J. Am. Chem. Soc.* 121, 9907–9914

Orally active GPIIb/IIIa-receptor antagonists

Several serious cardiovascular conditions, such as unstable angina and myocardial infarction, are associated with

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