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.

Monitor Editorship

After many years as our *Monitor Editor*, Andrew Lloyd has decided to hand on the role. Andrew has been an outstanding Editor for the *Monitor* section over the years and has played a crucial role in launching, sustaining and evolving the journal to the excellent standard that it is today.

On behalf of the editorial team and the readers, I would like to thank Andrew for his support, enthusiasm and contributions to the journal since its inception. It has been a pleasure working with him.

We wish him good luck for the future and for his new role as Professor of Biomedical Materials at the University of Brighton, UK. In the meantime, please send all ideas, proposals, outlines and articles for *Monitor* to: Debbie Tranter, Editor, *Drug Discovery Today*, 84 Theobald's Road, London, UK WC1X 8RR. e-mail: deborah.tranter@current-trends.com

Debbie Tranter
Editor
Drug Discovery Today

Farewell....

As the last member of the original team who brought you the first issue of *Drug Discovery Today*, I have finally decided to pass on the 'Monitor' chalice. Having been involved from an embryonic stage, it has been particularly rewarding to be part of the conception, birth and development of such an important internationally acclaimed journal. I would like to thank everyone who has supported me over the recent years with regular contributions, feedback and 'Profiles'. In particular, I'd like to thank the editorial and advertising support teams at Elsevier with whom I have had the pleasure of working. The journal is now entering a new era under the guidance of an exceptionally talented editorial team – I wish them all the very best for the future and hope they get as much enjoyment out of contributing to the dynamic force in drug discovery as I have done over the past 5 years.

Andrew Lloyd

Molecules

Dual sodium and calcium channel blocker with antioxidant activity

The progressive and delayed death of nerve cells following cerebral injury and cerebrovascular diseases, such as stroke, has been associated with a rise in intracellular calcium ion concentration as a consequence of the failure of intracellular energy-dependent ion homeostasis. This calcium ion overload results in a cascade process resulting in disorders of mitochondrial function and activation of calcium ion dependent enzymatic reactions. The calcium ion activation of nitric oxide synthase, phospholipase A_2 and xanthine oxidase also causes an increase in the degeneration of reactive

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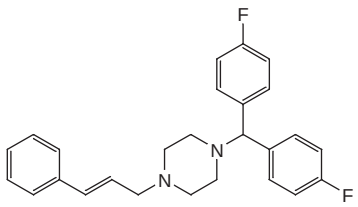
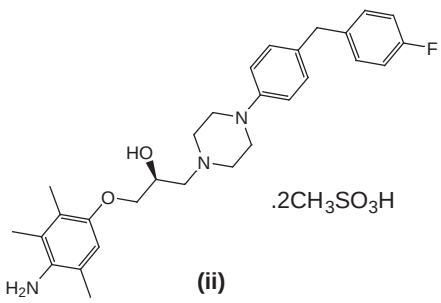
oxygen species that cause irreparable cell membrane damage through lipid peroxidation. The continual perpetuation of this process ultimately results in cell death.

Although several therapies, including the use of antioxidants, AMPA receptor antagonists and sodium and/or calcium channel blockers, are presently under clinical evaluation, these agents tend only to regulate a single pathway in the ischemic cascade and have yet to be shown to offer clinical benefit[1]. However, a recent paper has reported the benefit of using a combination of these compounds, each with a different therapeutic target, in the treatment of ischemia in animal models[2]. As part of a programme to develop novel agents for the treatment of ischemic stroke, based on the modification of a flunarizine template (**i**), workers at Suntory Biomedical Research (Osaka,



(i)

Japan) have reported the discovery of a candidate compound (2*S*)-1-(4-amino-2,3,5-trimethylphenoxy)-3-{4-[4-(4-fluorobenzyl)phenyl]-1-piperazinyl}-2-propanol dimethanesulfonate[3] (**ii**).



(ii)

This novel neuroprotectant has been shown to block both neuronal sodium ion and T-type calcium ion channels and acts as a powerful antioxidant. Evaluation in an *in vivo* transient middle-cerebral-artery occlusion model indicated that this agent has pronounced neuroprotective efficacy against neuronal damage induced by transient focal ischemia in rats. This compound might therefore have greater clinical efficacy for the treatment of acute ischemic stroke than other agents with a single mechanism of action in preventing neuronal cell damage.

1 Koroshetz, W.J. *et al.* (1996) Emerging treatments for stroke in humans. *Trends Pharmacol. Sci.* 17, 227–233

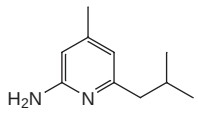
2 De Keyser, J. *et al.* (1999) Clinical trials with neuroprotective drugs in acute ischaemic stroke: are we doing the right thing? *Trends Neurosci.* 22, 535–540

3 Annoura, H. *et al.* (2000) Discovery of (2*S*)-1-(4-amino-2,3,5-trimethylphenoxy)-3-{4-[4-(4-fluorobenzyl)phenyl]-1-piperazinyl}-2-propanol dimethanesulfonate (SUN N8075): a dual Na^+ and Ca^{2+} channel blocker with antioxidant activity. *J. Med. Chem.* 43, 3372–3376

Nitric oxide synthase inhibitors

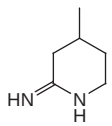
Nitric oxide is now well established as a ubiquitous mediator of both normal and pathophysiological processes. Nitric oxide is produced by the oxidation of L-arginine by three isoforms of nitric oxide synthase: the constitutively expressed neuronal nitric oxide synthase (nNOS), the endothelial cell nitric oxide synthase (eNOS) and the inducible nitric oxide synthase (iNOS). The neuronal form, nNos, is involved in the production of nitric oxide as a neurotransmitter, whereas eNOS regulates blood pressure and vascular tone through the production of nitric oxide in the vascular endothelium and iNOS expression is stimulated by a variety of inflammatory mediators through their activation of macrophages. The inflammatory induction of iNOS and the prolonged production of nitric oxide by activated inflammatory cells supports the view that this isoform has an important role in host defence and tissue damage associated with acute and chronic inflammation. This isoform might therefore have a role in diseases such as sepsis, arthritis and inflammatory bowel disease.

As part of a programme to identify potent and selective inhibitors of iNOS, Hagmann, W.K. and co-workers have prepared and evaluated a series of substituted 2-aminopyridines[4]. The most potent and selective inhibitors of iNOS were the 4-alkyl and 4,6-dialkyl derivatives. The most potent analogue was found to be (**iii**), which possessed an



(iii)

IC_{50} value of 28 nM and a fourfold selectivity for iNOS over nNOS. Further studies, however, revealed that the 2-aminopyridine analogues were not as potent or selective as their saturated counterparts, the 2-iminopiperidines, exemplified by (**iv**), (IC_{50} = 16 nM).



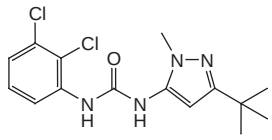
(iv)

4 Hagmann, W.K. *et al.* (2000) Substituted 2-aminopyridines as inhibitors of nitric oxide synthases. *Bioorg. Med. Chem. Lett.* 10, 1975–1978

p38 kinase inhibitors

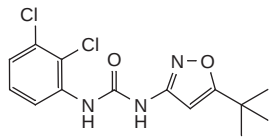
The MAP kinase p38 is known to have a role in cytokine signalling. Inhibitors of this enzyme have been shown to be effective *in vivo* models of endotoxic shock and arthritis and might also play a role in the treatment of osteoporosis.

Dumas, J. and co-workers have recently reported the identification of a series of potent, novel small-molecule inhibitors of p53 (Ref. 5). The lead compound (**v**), identified through a



(v)

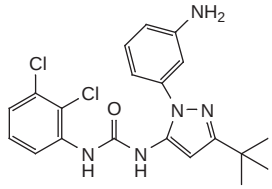
combinatorial screening programme, had an IC_{50} value of 53 nM. Replacement of the pyrazole ring provided the opportunity to broaden the scope of the libraries to isoxazolyl and thienyl ureas. Compounds (**v**) and (**vi**) were



(vi)

also found to be active in the submicromolar range in functional assays of cellular cytokine signalling involving TNF- and IL-1-induced IL-6 production in SW1353 cells.

In a second paper from this group, Dumas, J. and co-workers have identified several 2,3-dichlorophenyl ureas as small-molecule inhibitors of p38 (Ref. 6). Lead optimization has led to the discovery of a new class of potent and selective p38 kinase inhibitors exemplified by the 1-phenyl-5-pyrazolyl urea (**vii**) (IC_{50} = 13 nM).



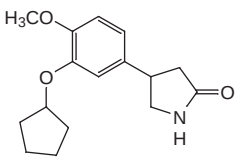
(vii)

5 Dumas, J. *et al.* (2000) Discovery of a new class of p38 kinase inhibitors. *Bioorg. Med. Chem. Lett.* 10, 2047–2050

6 Dumas, J. *et al.* (2000)1-Phenyl-5-pyrazolyl ureas: potent and selective p38 kinase inhibitors. *Bioorg. Med. Chem. Lett.* 10, 2051–2054

PDE4 inhibitors

The cAMP-specific phosphodiesterase type 4 (PDE4), found in inflammatory cells and smooth muscle, catalyses the deactivation of cAMP by hydrolysis of the phosphodiester bond. Increasing the cellular levels of cAMP through the inhibition of PDE4 results in the activation of protein kinases that downregulate inflammatory cell activity and relaxation of airway smooth muscle. PDE4 inhibitors have therefore become an attractive target for the development of therapeutic agents for the treatment of asthma. Early PDE4 inhibitors, such as rolipram (**viii**), have been shown to cause

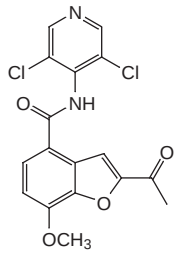


(viii)

nausea and emesis owing to an interaction with a secondary binding site known as the rolipram binding site. A second problem lies in the binding of some agents to PDE3, which can result in cardiotoxicity.

As part of a programme to identify PDE4 inhibitors for selectivity for the catalytic binding site over the rolipram binding site and for selectivity for PDE4 over PDE3, Buckley, G. and co-workers have investigated the synthesis and pharmacological profile of a novel series of 7-methoxybenzofuran-4-carboxamides as potential selective PDE4 inhibitors[7].

The most potent of these compounds was compound (**ix**), which had an IC_{50} value of 1.6 nM and good selectivity for the catalytic site over the rolipram binding site. Evaluation of this compound in the guinea-pig-skin eosinophilis model demonstrated good activity



(ix)

across a broad range of mediators. Neither emesis nor CNS effects were observed for this compound in the ferret emesis model when dosed orally with 10 mpk. Further optimization of this lead compound has the potential to provide a more efficacious agent with fewer side effects than that presently available.

7 Buckley, G. *et al.* (2000) 7-Methoxybenzofuran-4-carboamides as PDE 4 inhibitors: a potential treatment for asthma. *Bioorg. Med. Chem. Lett.* 10, 2137–2140

Emerging molecular targets

Gp130-mediated signalling as a therapeutic target

The pleiotropic cytokine IL-6 regulates haematopoiesis, inflammation and the immune response. The IL-6 receptor comprises an α chain (IL-6Rα) and a gp130 subunit. The binding of IL-6 to its receptor causes homodimerization of gp130, which, in turn, causes activation of Janus kinases resulting in subsequent activation of a variety of signal transduction pathways, including those mediated by signal tranducer SHP2 and transcriptional activator STAT3.

Because the overexpression of IL-6 and activation of gp130 have been implicated in the pathology of several diseases, including rheumatoid arthritis, juvenile chronic arthritis, multiple myeloma and plasmacytoma, Castleman's disease and Kaposi's sarcoma, the IL-6 activation pathway represents a potential therapeutic target for the treatment of such conditions. A recent review from

Ohtani, T. and co-workers provides a useful insight into this field[1] and describes the various approaches to inhibiting the activation of this pathway, including interfering with the formation of the IL-6/IL-6Rα/gp130 complex. The review includes coverage of neutralizing protein-based approaches, cytokine therapy and development of artificial cytokines based on the 'receptor conversion model'. The paper concludes by discussing the central role of STAT3 in pathogenesis and the importance of controlling STAT3 through future therapies focusing on the induction of negative regulatory molecules and the use of chimeric antibodies.

1 Ohtani, T. *et al.* (2000) gp130 mediates signalling as a therapeutic target. *Emerg. Ther. Targets* 4, 459–479

Insulin kinase receptor

Type II diabetes mellitus is characterized by a lack of response to insulin. The study of the mechanism of insulin action has led to the identification of the insulin receptor as a tyrosine kinase. A recent review describes the modulation and therapeutic implications of this insulin receptor kinase[2].

In summary, binding of insulin results in rapid activation of the insulin receptor kinase leading to the autophosphorylation of a receptor tyrosine residue and the potential to phosphorylate other cellular substrates. The activation of insulin receptor kinase by peroxovanadium compounds in the absence of insulin, leading to the full activation of the insulin cascade, together with studies on mutant insulin receptor kinases indicate that the insulin receptor kinase function is both necessary and sufficient for insulin signalling. Following activation, the insulin receptor kinase is rapidly internalized within the endosomal apparatus of the cell where it is capable of maintaining insulin signalling; the modulation of insulin receptor kinase within the endosome therefore represents a means of import to modulate insulin signalling. In fact, in recent years several endosomal processes have been shown to regulate insulin receptor kinase activity including a specific insulin protease (endosomal acidic insulinase) and an insulin receptor kinase-associated phosphotyrosine phosphatase that dephosphorylates and inactivates the insulin receptor kinase. Because both endosomal acidic insulinase and the insulin receptor kinase-associated phosphotyrosine phosphatase limit the duration and extent of insulin activity, inhibitors of these enzymes might be suitable therapeutic targets for the future development of agents for the treatment of insulin resistance.

2 Posner, B.I. (2000) The insulin receptor kinase: modulation and therapeutic implications. *Emerg. Ther. Targets* 4, 541–549

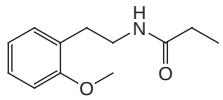
Andrew Lloyd

Combinatorial chemistry

Melatoninergic ligands

Melatonin (*N*-acetyl-5-methoxytryptamine) is the vertebrate pineal gland hormone secreted during darkness, which regulates the circadian rhythm in a large number of animals and in humans. Melatonin can be used to control diseases associated with circadian rhythm disorder and also alleviates jetlag, regulates delayed-sleep-phase syndrome and induces sleep. Conversely, it has been implicated in seasonal and winter depression and has also been reported to have anti-proliferative effects on mammary cell lines. It has been demonstrated that several of the effects of melatonin are mediated through G-protein-coupled receptors, and coupling to one of the G_i family of G proteins appears to be the common signalling pathway for the receptors characterized to date. Cloning studies reveal two recombinant mammalian melatonin receptors termed mt_1 and MT_2. The design and preparation of molecules selective for these receptors are important steps for their pharmacological characterization. A solid-phase mix and split approach was used to identify compounds that are capable of mimicking or antagonizing the response to melatonin[1].

A library of 108 compounds in mixtures of 12 was prepared on a Merrifield-based solid-phase resin and, following iterative re-synthesis of individual compounds from active mixtures, one of the most potent and selective compounds identified was (**i**), which had a K_i value of 6.56 nM (human MT_2)



(i)

and was 12-fold selective over human mt_1 (K_i = 81.2 nM). This library has enabled the exploration of affinities of the phenylalkylamido derivatives, exemplified by (**i**), for the human melatoninergic receptors mt_1 and MT_2. Several structural features have been determined that lead to high potency, such as the favoured propyl side-chain seen in (**i**).

1 Langlois, M. *et al.* (2000) Synthesis of a small library of phenylalkylamide derivatives as melatoninergic ligands for human mt_1 and MT_2 receptors. *Bioorg. Med. Chem. Lett.* 8, 163–171

Inhibition of galactose-binding proteins

Despite a growing appreciation of the importance of complex carbohydrates in medicinally relevant receptor–ligand interactions, few carbohydrate-based drugs have reached the market. This is partly because of the polar and hydrolytically labile nature of carbohydrates, in addition to the fact that monovalent interactions between carbohydrates and proteins are often of low affinity. Nature usually uses polyvalency to ensure high affinity. A solution-phase parallel approach has been used to discover small molecules inhibiting

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