Monitor: molecules and profiles

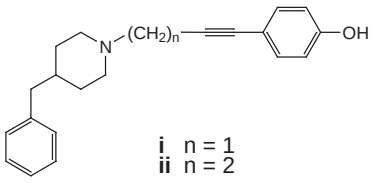
Monitor provides an insight into the latest developments in drug discovery through brief synopses of recent presentations and publications together with expert commentaries on the latest technologies. There are two sections: *Molecules* summarizes the chemistry and the pharmacological significance and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

Subtype-selective NMDA-receptor ligands

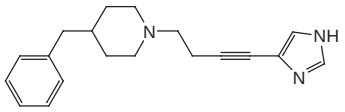
High concentrations of the excitatory neurotransmitter L-glutamic acid (glutamate) released, for example, during ischaemic events, are known to be neurotoxic. This toxicity appears to be associated with activation of *N*-methyl-D-aspartate (NMDA) receptors, as antagonists of these receptors can offer neuroprotection in animal models of focal ischaemia. Similar studies have shown that the over-activation of these NMDA-associated glutamate pathways might also be important in Parkinson's disease. Mammalian NMDA-receptors are ligand-gated ion channels composed of NR1 and NR2 subunits. The development of subtype-selective NMDA-receptor antagonists could reduce the side effects associated with their non-selective counterparts. Wright, J.L. and coworkers have recently described the potent antagonists (**i**) and (**ii**) (Ref. 1). Intraperitoneal administration of these agents potentiates the effects of L-DOPA in a rat model of Parkinson's disease but has little biological activity alone.

A more recent paper from the same group describes the effects of replacing



i n = 1
ii n = 2

the phenol moiety in (**i**) and (**ii**) with a pyrrole, pyrazole or imidazole group on NR1A/2B potency and *in vivo* activity[2]. These studies have led to the identification of 4-benzyl-1-[4-(1*H*-imidazol-4-yl)but-3-ynyl]piperidine (**iii**)



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as a potent antagonist of this subclass of NMDA receptor. This compound potentiates the effects of 3 mg kg^{-1} L-DOPA administered orally in the 6-hydroxydopamine-lesioned rat model of Parkinson's disease, indicating both acceptable bioavailability and CNS penetration of this compound.

1 Wright, J.L. *et al.* (1999) Subtype-selective *N*-methyl-D-aspartate receptor antagonists: Synthesis and biological evaluation of 1-(arylalkynyl)-4-benzylpiperidines. *J. Med. Chem.* 42, 2469–2477

2 Wright, J.L. *et al.* (1999) Discovery of subtype-selective NMDA receptor ligands: 4-benzyl-1-piperidinylalkynylpyrroles, pyrazoles and imidazoles as NR1A/2B antagonists. *Bioorg. Med. Chem. Lett.* 9, 2815–2818

Purine nucleoside phosphorylase inhibitors

Purine nucleoside phosphorylase catalyzes the reversible phosphorolysis of ribo- and 2′-deoxyribonucleosides of guanine and hypoxanthine in higher organisms. Purine nucleoside phosphorylase inhibitors could therefore be useful in several therapeutic areas including T-cell proliferative diseases (such as T-cell leukemia) and in prolonging the half-lives of certain chemotherapeutic agents that are deactivated by purine nucleoside phosphorylases. The reversible phosphorylation is achieved via a tertiary complex involving the purine nucleoside phosphorylase enzyme, the nucleoside and orthophosphate. Although several metabolically stable acyclic nucleotide analogues have been synthesized as multi-substrate analogue inhibitors of purine nucleoside phosphorylase, no compound has yet reached clinical trials. The most potent and structurally simple purine

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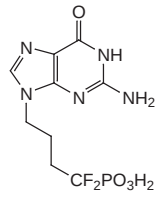
nucleoside phosphorylase inhibitor reported so far is 9-(5,5′-difluoro-5′-phosphonopentyl)guanine (**iv**).



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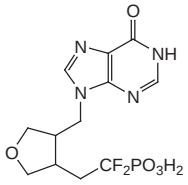

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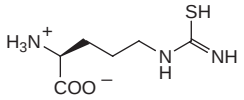
A recent paper by Yokomatsu, T. and coworkers has described the synthesis of conformationally constrained *cis*- and *trans*-analogues of this compound (**v**) (Ref. 3). Both analogues are potent inhibitors of purine nucleoside phosphorylase isolated from *Cellulomonas* sp. with IC_{50} values of 35 and 37 nM, respectively. However, the *cis*-isomer is a more potent inhibitor of human erythrocyte purine nucleoside phosphorylase (IC_{50} = 88 nM) than either the *trans*-isomer (IC_{50} = 320 nM) or compound (**iv**) (IC_{50} = 380 nM).

3 Yokomatsu, T. *et al.* (1999) Synthesis and biological evaluation of 1,1-difluoro-2-(tetrahydro-3-furanyl)ethylphosphonic acids possessing a N9-purinylmethyl functional group at the ring. A new class of inhibitors for purine nucleoside phosphorylases. *Bioorg. Med. Chem. Lett.* 9, 2833–2836

Nitric oxide synthase inhibitor

Nitric oxide is an important chemical messenger mediating many effects associated with maintaining cardiovascular homeostasis in different tissues. The agent is produced biosynthetically from L-arginine by nitric oxide synthase (NOS). There are two types of NOS isoforms, the constitutive calcium/calmodulin-dependent type (cNOS), which can be further divided into the neuronal form (nNOS) and the endothelial form (eNOS), and the inducible calcium/calmodulin-independent type (iNOS). Tissue- and isoform-selective NOS inhibitors offer the potential to develop agents for the specific treatment of many nitric oxide-mediated conditions. A recent paper from Ulhaq, S. and coworkers describes an investigation into the structure–activity relationships of L-thiocitrulline (**vi**), a known potent inhibitor of several nitric oxide synthase isoforms[4].



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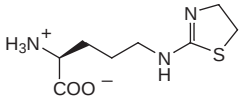

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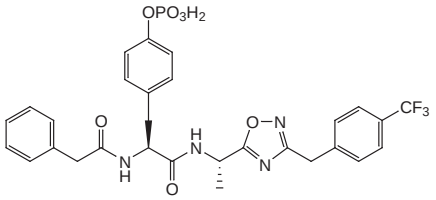
These studies have led to the identification of N^{δ}-(4,5-dihydrothiazol-2-yl)ornithine (**vii**) as a potent inhibitor of rat iNOS (IC_{50} = 8.1 μM) and nNOS (IC_{50} = 4.3 μM), and cNOS derived from a human tumour xenograft (IC_{50} = 1.3 μM). The group is presently investigating the development of tissue-specific prodrugs to enhance the site-specific delivery of this agent.

4 Ulhaq, S. *et al.* (1999) Heterocyclic analogues of L-citrulline as inhibitors of the isoforms of nitric oxide synthase (NOS) and identification of N^{δ}-(4,5-dihydrothiazol-2-yl)ornithine as a potent inhibitor. *Bioorg. Med. Chem.* 7, 1787–1796

Tyrosine kinase ZAP-70 inhibitors

The protein tyrosine kinase ZAP-70 has an important role in T-cell function *in vivo* in knockout mice and in humans with disrupted ZAP-70. In both instances, the absence of T-cell function caused by suppression of the enzyme compromises the immune response. This enzyme might, therefore, be a useful therapeutic target for the development of novel immune suppressants. The enzyme consists of two tandem SH2 domains of approximately 100 amino acids, which preferentially bind to specific tyrosine-phosphorylated proteins. Workers from ARIAD Pharmaceuticals (Cambridge, MA, USA) have recently reported the discovery of a series of 1,2,4-oxadiazole analogues, exemplified by (**viii**), as potent and selective SH2-related inhibitors of this enzyme[5]. This group of compounds has a high selectivity for ZAP-70 over the closely related tyrosine kinase SYK and other SH2-containing peptides such as SRC and GRB2. Gel-shift studies indicate that these compounds interact with the C-terminal of the ZAP-70 SH2. The group is presently using these compounds as leads for the development of ZAP-70 inhibitors for cellular studies.



viii

5 Vu, C.B. *et al.* (1999) Discovery of potent and selective SH2 inhibitors of the tyrosine kinase ZAP-70. *J. Med. Chem.* 42, 4088–4098

Combinatorial chemistry

Melanocortin-1 receptor agonists

The melanocortin peptides that include the α-, β-, γ-melanocyte-stimulating hormones (MSH) and adrenocorticotrophin (ACTH) all possess a His-Phe-Arg-Trp epitope known as the 'message' sequence. These peptides are responsible for a range of physiological actions including skin pigmentation, energy

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