Monitor: molecules and profiles

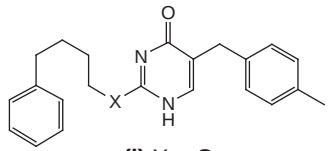
Monitor provides an insight into the latest developments in drug discovery through brief synopses of recent presentations and publications together with expert commentaries on the latest technologies. There are two sections: *Molecules* summarizes the chemistry and the pharmacological significance and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

Lipoprotein-associated phospholipase A_2 inhibitors

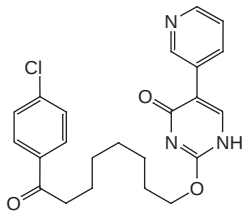
The hydrolysis of oxidatively modified phosphorylcholines by lipoprotein-associated phospholipase A_2 leads to the release of proinflammatory oxidized fatty acids and lysophophatidylcholine. These products have been implicated in atherosclerosis. The inhibition of lipoprotein-associated phospholipase A_2 might therefore offer an attractive approach to antiatherosclerotic therapy.

A recent paper from workers at SmithKline Beecham Pharmaceuticals (Harlow, Essex, UK) describes how the HTS of their compound databank led to the identification of pyrimidones (**i**) and (**ii**) as weak (IC_{50}s = 12 and 55 μM, respectively), reversible inhibitors of lipoprotein-associated phospholipase A_2 (Ref. 1).



(i) X = O
(ii) X = S

Subsequent optimization of these lead compounds led to the identification of a novel series of highly potent and selective lipoprotein-associated phospholipase A_2 inhibitors exemplified by (**iii**) (IC_{50} = 64 nM).



(iii)

Unlike other known inhibitors, these compounds are competitive inhibitors of the enzyme. These agents will be useful tools in the further evaluation of the role of lipoprotein-associated phospholipase A_2 in atherosclerosis.

1 Boyd, H.F. *et al.* (2000) 2-Alkylthiopyrimidin-4-ones as novel, reversible inhibitors of lipoprotein-associated phospholipase A_2. *Bioorg. Med. Chem. Lett.* 10, 395–398

Human cytosolic phospholipase A_2 inhibitors

A group from Shionogi Research Laboratories (Osaka, Japan) have focussed on developing inhibitors of cytosolic phospholipase A_2. The cytosolic phospholipase A_2 comprises three different types of enzyme: α, β and γ. The 85 kDa α enzyme is characterized by a calcium-dependent lipid-binding domain and a catalytic domain. The enzyme requires micromolar concentrations of calcium ions for membrane translocation and, unlike the less specific phospholipase A_2 enzymes, has a specificity for arachidonic acid bound to the *sn*-2 position of phospholipids. This suggests that cytosolic phospholipase A_2 is involved in the production of eicosanoids. Studies in cytosolic phospholipase A_2-deficient mice support this hypothesis and indicate that cytosolic phospholipase A_2 plays an important role in inflammation and reperfusion injury. Inhibitors of cytosolic phospholipase A_2 might therefore be useful therapeutic agents for the treatment of inflammatory diseases and stroke.

As part of a screening programme, Seno, K. and coworkers identified the two nonpeptide low-MW cytosolic phospholipase A_2 inhibitors (**iv**) and (**v**) with IC_{50} values of 1.5 and 1.7 μM, respectively[2].

Through the combination of these two structures and subsequent structure–activity optimization using both enzyme

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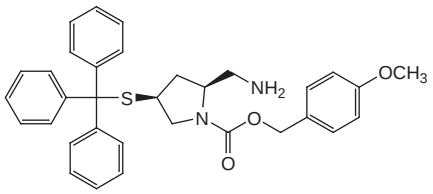

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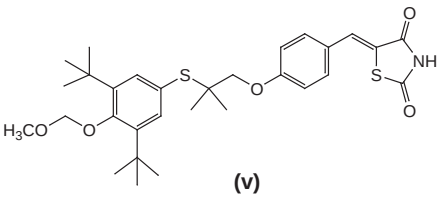
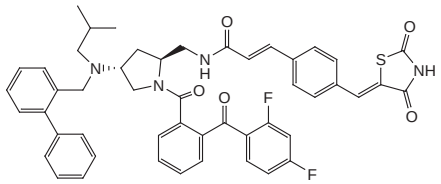


(v)

assays and secondary cell-based assays designed to select membrane-penetrating inhibitors specific for arachidonic acid release, the group has identified a series of highly potent 1,2,4-trisubstituted pyrrolidine based inhibitors exemplified by (**vi**) (IC_{50} = 1.8 nM).



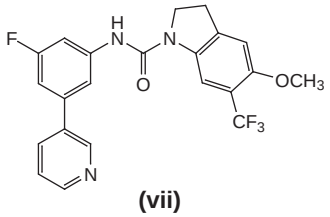
(vi)

2 Seno, K. *et al.* (2000) Pyrrolidine inhibitors of human cytosolic phospholipase A_2. *J. Med. Chem.* 43, 1041–1044

5-HT_{2C}-receptor inverse agonists: potential antidepressant/ anxiolytic agents

Selective 5-$HT_{2C/B}$-receptor antagonists have previously been shown to exhibit significant anxiolytic activity in animal models. Recent data has also suggested that 5-HT_{2C}-receptor antagonists could be useful therapeutic agents for the treatment of other CNS disorders such as depression, schizophrenia, migraine and Parkinson's disease. As part of a programme to develop 5-HT_{2C}-receptor ligands, workers from SmithKline Beecham Pharmaceuticals (Harlow, Essex, UK) have reported the evolution, synthesis and biological activity of a novel series of 5-HT_{2C}-receptor inverse agonists that abolish basal activity in a functional assay using human cloned 5-HT_{2C} receptors[3].

A series of biarylcarbamoylindolines, with excellent 5-HT_{2C}-receptor affinity and selectivity over 5-HT_{2A} receptors, and a series of (pyridyloxypyridyl)-carbamoylindolines offering additional selectivity over the closely related $5HT_{2B}$ receptors were investigated. Following evaluation of oral activity in a rat *m*-chlorophenylpiperazine hypolocomotion model and in animal models of anxiety, compounds (SB228357, **vii**) and (SB243213, **viii**) have been selected for further evaluation as novel non-sedating antidepressant/anxiolytic agents.



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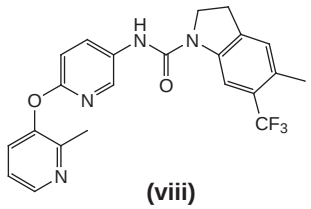


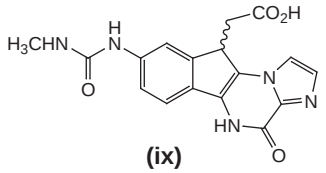
(viii)

3 Bromidge, S.M. *et al.* (2000) Biarylcarbamoylindolines are novel and selective 5-HT_{2C} receptor inverse agonists: identification of 5-methyl-1-[[2-[(2-methyl-3-pyridyl)oxy]-2-pyridyl]carbamoyl]-6-trifluoromethylindoline (SB-243213) as a potential antidepressant/anxiolytic agent. *J. Med. Chem.* 43, 1123–1134

Highly potent *in vivo* AMPA-receptor antagonists

The major fast excitatory neurotransmitter L-glutamate activates three major postsynaptic ionotropic receptors, NMDA, AMPA and kainate receptors. With the recent identification of a link between glutamate activation, neurodegeneration and cell death, there has been increased interest in the identification of glutamate-receptor antagonists that might have therapeutic application in the treatment of neurological disorders.

Mignani, S. and coworkers have reported the synthesis and evaluation of a novel series of water-soluble 8-methylureido-4,5-dihydro-4-oxo-10*H*-imidazo-[1,2-*a*]indeno[1,2-*e*]pyrazines as potential AMPA-receptor ligands[4]. Compounds (**ix**) [(+)-isomer] and (**x**) were found to have high affinity (IC_{50} = 4 and 9 nM, respectively) for the ionotropic AMPA receptor and were shown to be



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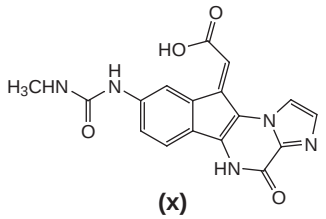

(x)

highly potent receptor antagonists (IC_{50} = 2 and 3 nM, respectively). Evaluation of the *in vivo* anticonvulsant activity of these agents against both electrically and sound-induced convulsions in mice after intraperitoneal, subcutaneous and intravenous administration (ED_{50} $\leqslant$11 mg kg^{-1}) suggested that these compounds have excellent blood–brain barrier penetration associated with high anticonvulsant activity.

4 Mignani, S. *et al.* (2000) 8-Methylureido-4,5-dihydro-4-oxo-10*H*-imidazo[1,2-*a*]indeno[1,2-*e*]pyrazines: Highly potent *in vivo* AMPA antagonists. *Bioorg. Med. Chem. Lett.* 10, 591–596

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