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# 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.

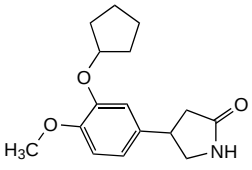


## Molecules

### Phosphodiesterase type 4 inhibitors with reduced side effects

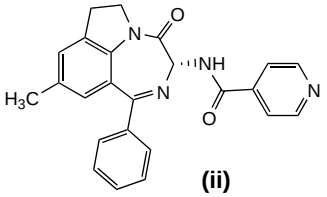
Phosophodiesterases are a family of enzymes that hydrolyze the second messengers cAMP or cGMP thus regulating their intracellular concentration. The phosphodiesterases have been categorized into subtypes and type 4 (PDE 4) is specific for cAMP. PDE 4 is found within inflammatory cells and airway smooth muscle and is thus a potential target for anti-asthmatic and anti-inflammatory drugs.

Various inhibitors of PDE 4 have exhibited efficacy in a range of inflammatory models; however, first generation inhibitors, such as Rolipram **(i)**, induce side effects including nausea and emesis. Efforts to improve the therapeutic window of PDE 4 inhibitors have focussed on improving the potency of the inhibition of enzyme activity and reducing affinity for the so-called high affinity Rolipram binding site.

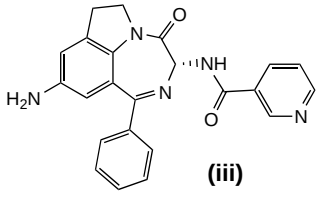


**(i)**

A Pfizer group (Fresnes, France) previously identified PDE 4 inhibitor **(ii)** as a candidate for clinical development[1]. However, efforts to improve on the molecule were continued and later an extensive SAR optimization program identified molecule **(iii)** as a back up candidate[2]. Molecule **(iii),** CI1044, has improved potency against PDE 4 in human cells [$IC_{50}$ = 0.27 μM for **(iii)** and 1.1 μM for **(ii)**] and is inactive against PDE types 1, 3 and 5.



**(ii)**



**(iii)**

Replacement of the methyl group of the molecules with an amino group resulted in improved ability to reduce the release of the cytokine tumour necrosis factor-alpha (TNF-α) from both human peripheral blood monocytes [$IC_{50}$ = 0.34 μM for **(iii)** compared with 0.99 μM for **(ii)**] and particularly human whole blood [$IC_{50}$ = 0.84 μM for **(iii)** and 61 μM for **(ii)**]. Upon oral administration, molecule **(iii)** also inhibited antigen-induced eosinophil recruitment to the lung with an $ED_{50}$ value of 3.2 mg $kg^{-1}$ in the rat. When molecule **(iii)** was administered intravenously to ferrets, in contrast to Rolipram, no emetic or retching events were observed. This is consistent with the observed low binding to the high affinity Rolipram binding site [$IC_{50}$ = 1.7 μM for **(iii)** and 0.005 μM for Rolipram].

1 Pascal, Y. *et al.* (2000) Synthesis, structure–activity relationships of 4-oxo-1-phenyl-3,4,6,7-tetrahydro[1,4] diazepino[6,7,1-*hi*]indoles: novel PDE4 inhibitors. *Bioorg. Med. Chem. Lett.* 10, 35–38

2 Burnouf, C. *et al.* (2000) Synthesis, structure–activity relationships and pharmacological profile of 9-amino-4-oxo-1-phenyl-3,4,6,7-tetrahydro[1,4]diazepino[6,7,1-*hi*]indoles: discovery of potent, selective phosphodiesterase inhibitors. *J. Med. Chem.* 43, 4850–4867

### Adenosine kinase inhibitors

One of the many functions of adenosine in the body is to act as an extracellular messenger that binds to specific cell surface receptors, the P1 purinergic receptors, and modulates neuronal activity and inflammation. Adenosine agonists given systemically or intraspinally have provided pain relief in several clinical and preclinical settings, particularly for neuropathic pain. Despite extensive efforts, the direct modulation of adenosine receptors with agonists has not thus far provided drug candidates, mainly owing to mechanism-based side effects.

Adenosine kinase (AK) is a key enzyme in regulating the levels of intra- and



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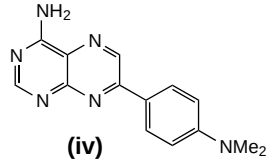
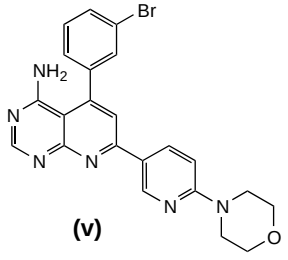
extra-cellular adenosine. It is an intracellular enzyme that catalyzes the phosphorylation of adenosine to adenosine monophosphate (AMP), presumably trapping it within the cell. Inhibition of AK augments the concentration and effect of adenosine locally at sites of injury. This indirect approach might avoid the actions of adenosine in other tissues and thus give a greater therapeutic margin.

A group at Abbott Laboratories (Abbott Park, IL, USA) identified the screening hit **(iv)** as an inhibitor of AK with an $IC_{50}$ value of 400 nM (Ref. 3). Molecule **(iv)** was chosen as a starting point for optimization rather than the natural ligand adenosine because it lacked the polar sugar unit and is thus more likely to give membrane penetration and improve metabolic stability.




**(iv)**

Altering the 1,4-pyrazine ring to a pyridine allowed groups to be incorporated at position 5, which greatly improved potency. Changing the phenyl ring to a pyridine results in improved water solubility and leads to a series of molecules exemplified by compound **(v)**. Molecule **(v)** inhibited cytosolic AK with an $IC_{50}$ value of 2 nM and, in an intact cell based assay, inhibited AK with an $IC_{50}$ value of 50 nM. Upon oral administration it is active in a thermal hyperalgesia model and a formalin test.




**(v)**

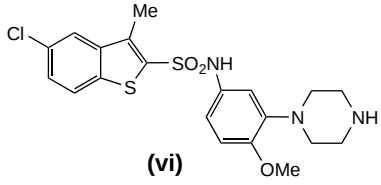
The series is being developed to identify potent oral analgesics and to gain selectivity over side effects shown by some analogues by reducing spontaneous locomotor activity.

**3** Cowart, M. *et al.* (2001) Structure–activity studies of 5-substituted pyridopyrimidines as adenosine kinase inhibitors. *Bioorg. Med. Chem. Lett.* 11, 83–86

### Selective 5-$HT_6$ antagonists for cognitive disorders

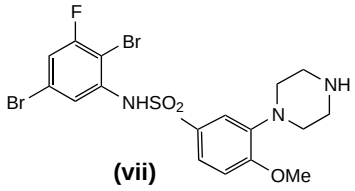
The 5-hydroxytryptamine (5-HT, serotonin) superfamily consists of seven classes of receptors and embraces 14 human subclasses. The latest to be cloned is the 5-$HT_6$ receptor, the biological function of which is poorly understood. However, its distribution in the brain, in addition to its high affinity for a variety of psychiatric drugs, has generated a great deal of interest with a potential role in the treatment of schizophrenia, depression and learning and memory disorders.

A group at SmithKline Beecham (Harlow, UK) previously reported the sulfonamide **(vi)** to be a potent 5-$HT_6$ antagonist in Phase I clinical trials for the treatment of cognitive disorders[4]. The group continued to study the SAR around the bisaryl-sulfonamides including the reverse sulfonamide exemplified by molecule **(vii)**[5].




**(vi)**

Substituted phenyl groups on the left-hand side were favoured in this series with 2- and 3-substitution giving improved potency over 4-substitution. Substitution at both positions 3 and 5 gave low clearance and high oral bioavailability but a low brain:blood ratio. CNS penetration was improved by substitution at position 2, with the 2,5-dibromo-3-fluoro analogue shown proving optimal. Molecule **(vii)** is a highly selective, competitive antagonist ($pK_i = 8.54$), with 19% CNS penetration, low clearance (14 ml $min^{-1}$ $kg^{-1}$) and good oral bioavailability (65%) in the rat. Attempts to improve the brain penetration, by cyclizing onto the polar sulfonamide NH, led to rapid clearance. On the basis of its biological profile, molecule **(vii)** (SB357134) has been selected for further clinical evaluation.




**(vii)**

**4** Bromidge, S. *et al.* (1999) 5-Chloro–*N*-(4-methoxy-3-piperazin-1-yl-phenyl)-3-methyl-2-benzothiophenesulphonamide (SB-271046): A potent,selective and orally bioavailable 5-$HT_6$ receptor antagonist. *J. Med. Chem.* 42, 202–205

**5** Bromidge, S. *et al.* (2001) Phenyl benzenesulphonamides are novel selective 5-$HT_6$ antagonists: identification of *N*-(2,5-dibromo-3-fluorophenyl)-4-methoxy-3-piperazin-1-ylbenzensulphonamide (SB-357134). *Bioorg. Med. Chem. Lett.* 11, 55–58

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## Novel antitumour molecules

### Polyamine analogues as chemotherapeutic agents

The polyamines spermidine, spermine and putrescine are polycationic compounds that are found in significant amounts in nearly every prokaryotic and eukaryotic cell type. Their biosynthetic pathways provide important targets for therapeutic intervention because depletion of polyamines results in the disruption of several cellular functions and, in specific cases, cytotoxicity. The role of terminally alkylated polyamines as antitumour and/or antiparasitic agents has been reviewed by researchers at Wayne

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