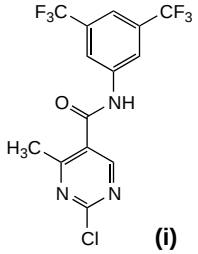
Monitor: molecules and profiles

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

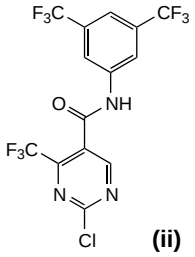
NF-κB and AP-1 gene expression inhibitors

Nuclear factor-kappa binding (NF-κB) transcription factor and activator protein-1 (AP-1) control the production of many of the cytokines and proteins involved in immunoinflammatory diseases. Activation of such transcription factors can result from several different external signals, including stress, infection and normal bioregulating molecules, and leads to their specific binding to DNA and upregulation of various gene products. NF-κB and AP-1 control the production of interleukins IL-1, IL-2, IL-6, IL-8 and tumour necrosis factor-alpha (TNF-α) and, as such, are attractive targets for new approaches to treating immunoinflammatory diseases. Recently, researchers from Signal Pharmaceuticals (San Diego, CA, USA) have described a SAR study that led to the identification of **(i)** as a potent dual inhibitor of NF-κB and AP-1 activation[1].



(i)

Earlier work by the same researchers[2] had previously identified compound **(ii)** as a potent inhibitor of AP-1 and NF-κB activation, which also displayed activity in inflammation and immunosuppression models after intraperitoneal administration at 10–20 mg kg^{-1} (Ref. 3). However, this compound was shown to have poor oral bioavailability, a feature confirmed by poor permeability in a Caco-2 cell-based assay. Using **(ii)** as a lead compound, the researchers used solution-phase combinatorial chemistry techniques to prepare ~3200 analogues to fully explore the SAR around the core structure and to identify compounds with improved oral absorption.



(ii)

Compound **(ii)** displayed inhibition of AP-1- and NF-κB-mediated transcriptional activation comparable with **(i)** in Jurkat cells [IC_{50} values: AP-1 = 0.02 μM and 0.05 μM; NF-κB = 0.05 μM and 0.05 μM, for **(i)** and **(ii)**, respectively], and also demonstrated improved Caco-2 permeability [$P_{app} = 62 \pm 6 \times 10^{-7}$ cm sec^{-1}: and $11 \pm 4 \times 10^{-7}$ cm sec^{-1} for **(i)** and **(ii)**, respectively].

1 Palanki, M.S.S. *et al.* (2000) Inhibitors of NF-κB and AP-1 gene expression: SAR studies on the pyrimidine portion of 2-chloro-4-trifluoromethylpyrimidine-5-{*N*-[3′,5′-bis(trifluoromethyl)-phenyl]carboxamide}. *J. Med. Chem.* 43, 3995–4004

2 Sullivan, R.W. *et al.* (1998) 2-Chloro-4-(trifluoromethyl)pyrimidine-5-*N*-[3′,5′-bis(trifluoromethyl)phenyl]-carboxamide: a potent inhibitor of NF-κB- and AP-1-mediated gene expression identified using solution-phase combinatorial chemistry. *J. Med. Chem.* 41, 413–419

3 Goldman, M.E. *et al.* (1996) SP100030 is a novel T-cell-specific transcription factor inhibitor that possesses immunosuppressive activity *in vivo*. *Transplant. Proc.* 28, 3106–3109

A natural product TNF-production inhibitor

Inhibition of the release of tumor necrosis factor (TNF) offers a potential approach for the treatment of various inflammatory diseases. As a complement to small-molecule TNF inhibitors, natural products offer the possibility of totally unprecedented structural types as scaffolds for subsequent optimization. Recently, Kakinuma and colleagues described the isolation of a novel series of quinolone natural products with a tricyclic structure. The major component, quinolactacin A **(iii)** was shown to dose-dependently inhibit bacterial lipopolysaccharide (LPS)-induced TNF production by murine peritoneal macrophage cells (IC_{50} = 12.2 μg ml^{-1})[4]. The quinolactacins were isolated from the fermentation broth of a fungal strain from the larvae of the mulberry pyralid, subsequently identified as a member of *Penicillium* sp., EPF-6. Although the gross structure was determined as shown **(iii)**, the absolute configuration remains to be elucidated[5].

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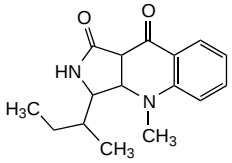


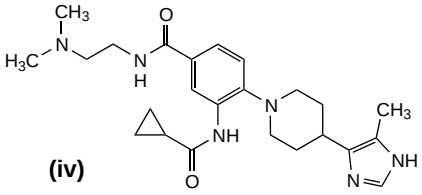
(iii)

4 Kakinuma, N. *et al.* (2000) Quinolactacins A, B and C: novel quinolone compounds from *Penicillium* sp. EPF-6. I. Taxonomy, production, isolation and biological properties. *J. Antibiot.* 53, 1247–1251

5 Takahashi, S. *et al.* (2000) Quinolactacins A, B and C: novel quinolone compounds from *Penicillium* sp. EPF-6. II. Physico-chemical properties and structure elucidation. *J. Antibiot.* 53, 1252–1256

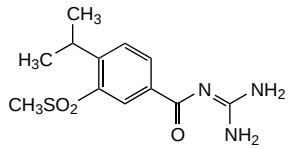
A novel sodium/hydrogen exchange inhibitor

The Na^{2+}/H^{+} exchanger regulates intracellular pH and is involved in cell injury resulting from ischaemia and reperfusion. Inhibitors of this exchanger are potentially attractive as cardioprotective agents for the treatment of ischaemia, because of their ability to prevent the accumulation of sodium and calcium ions. Recently, workers at Sanofi-Synthelabo (Cedex, France) identified compound **(iv)** as the first example of a new structural class of inhibitors of the NHE1 isoform of the ubiquitous Na^{2+}/H^{+} transporter[6].



(iv)

Cariporide **(v)** is a representative of the structurally distinct acylguanidine class of NHE1 inhibitors, whereas this newly identified compound **(iv)** is a novel imidazoylpiperidine. Biological activity was demonstrated by measuring the recovery of pH in NHE1- and NHE2-expressing CCL39-derived PS120-variant cells exposed to intracellular acid-load. Intracellular pH recovery was inhibited by **(iv)** with an IC_{50} value of 3.3 ± 1.3 nM for NHE1-expressing cells and an IC_{50} value of 2.3 ± 1.0 μM for NHE2-expressing cells. By contrast, cariporide showed respective IC_{50} values of 103 ± 28 nM (NHE1) and 73 ± 46 μM (NHE2).

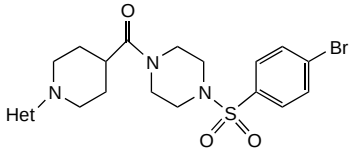


(v)

6 Lorrain, J. *et al.* (2000) Pharmacological profile of SL591227, a novel inhibitor of the sodium/hydrogen exchanger. *Br. J. Pharmacol.* 131, 1188–1194

Novel inhibitors of cholesterol biosynthesis

Successful therapy using the statin class of hypocholesterolemic agents has led to the search for other novel inhibitors of the cholesterol biosynthesis pathway. In particular, inhibitors of the squalene synthase (SQS) step have been considered. In addition to their work on SQS inhibitors, Brown and colleagues have recently investigated the inhibition of 2,3-oxidosqualene cyclase (OSC) and reported a series of 4-piperidinopyridine and 4-piperidinopyrimidine inhibitors of OSC **(vi)**[7].



Het = Pyridine, pyrimidine

(vi)

The compounds were tested orally in rats for inhibition of cholesterol biosynthesis. *In vivo* inhibition of OSC was confirmed by *in vitro* studies. Comparison of the two series indicated that the pyrimidine moiety afforded more potency to the compounds than the corresponding pyridino derivatives both *in vitro* and *in vivo*. The most interesting compounds were comparable with simvastatin, a clinically used hydroxymethylglutarylCoA (HMGCoA) reductase inhibitor. Because the pK_a values of the most interesting derivatives vary only slightly (pK_a = 6 and 7), the authors suggest that further novel OSC inhibitors might be found in either series by exploring a broader range of pK_a values (e.g. 5–9).

7 Brown, G.R. *et al.* (2000) A novel series of 4-piperidinopyridine and 4-piperidinopyrimidine inhibitors of 2,3-oxidosqualene cyclase-lanosterol synthase. *J. Med. Chem.* 43, 4964–4972

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Combinatorial chemistry

HIV-1 protease inhibitors

The HIV-1 protease is a member of the aspartic protease family of enzymes that produces essential structural and functional viral proteins by proteolytic processing of the *gag*- and *gag-pol* viral gene products. Protease inhibitors have shown clinical efficacy for the treatment of HIV-1 infection by reducing the plasma viral-load in infected individuals. However, rapid turnover of HIV-1 and the high frequency of mutations in the HIV genome eventually result in the selection of mutant strains and in the development of clinical resistance. Therefore, there is a requirement for the development of new HIV-1 protease inhibitors.

A solid-phase parallel synthesis approach was used for the generation of novel unsymmetrical protease inhibitors[1]. A small library of eight individual compounds was synthesized on 3,4-dihydro-2*H*-2-ylmethoxymethyl polystyrene solid-phase resin. The compounds were

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