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.**

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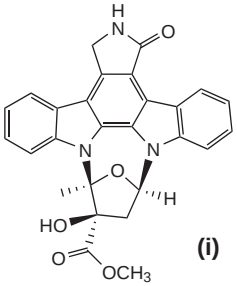
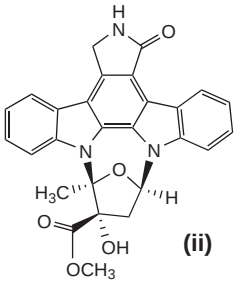
Molecules

Kinase inhibitory activity of 3′-(*S*)-*epi*-K252a

Compound (+)K252a (**i**), originally isolated from the culture broth of *Nocardiopsis* sp. [1], inhibits several serine–threonine and tyrosine kinases, such as protein kinase C (PKC), cAMP-dependent protein kinase (PKA), myosin light chain kinase (MLCK) and tyrosine kinase A receptor (TrkA) in a nanomolar range [2]. Its numerous functional activities include antitumour, antibiotic, anti-inflammatory and neuronal survival promoting [3]. Three analogues of compound **i**, namely CEP2563, CEP701 and CEP1347, have been developed at Cephalon (http://www.cephalon.com/) and are advancing into clinical trials [4]. Further examination of this template has recently led the same group [5] to the development of the diastereomer **ii**, to assess the role of the 3′-sugar alcohol on kinase potency and selectivity.



(i)



(ii)

Compound **ii** was synthesized by a four step synthesis from K252a. Accordingly, the ester group was reduced and the resulting diol was transformed into the corresponding ketone. The stereocentre was then formed by cyanide addition and subsequent transformation of the nitrile to the methyl ester.

The structure of compound **ii** was assigned on the basis of NMR data, along with COSY and HETCOR experiments. When tested for kinase inhibition, compound **i** had IC_{50} values of 13 nM and 43 nM against TrkA and vascular endothelial growth factor receptor (VEGFR2), respectively. In the same experiments, compound **ii** had IC_{50} values of 1.2 nM and 19 nM, respectively. In addition, compound **i** inhibited the serine–threonine kinases PKC and mixed-lineage protein kinase (MLK1) with IC_{50} values of 250 nM and 22 nM, respectively. For compound **ii**, the corresponding IC_{50} values were 114 nM and 25 nM, respectively.

These data indicate the presence of important stereochemical requirements at the sugar moiety for binding the above quoted kinases.

1 Kase, H. *et al.* (1986) K-252a, a potent inhibitor of protein kinase C from microbial origin. *J. Antibiot.* 39, 1059–1065
2 Kase, H. *et al.* (1987) K-252 compounds, novel and potent inhibitors of protein kinase C and cyclic nucleotide-dependent protein kinases. *Biochem. Biophys. Res. Commun.* 142, 436–440
3 Omura, S. *et al.* (1995) Staurosporine, a potentially important gift from a microorganism. *J. Antibiot.* 48, 535–548
4 Saporito, M. *et al.* (2002) In *Progress in Medicinal Chemistry* (Vol. 40), pp. 23, Elsevier Science
5 Gingrich, D.E. *et al.* (2002) Synthesis and kinase inhibitory activity of 3′-(*S*)-*epi*-K252a. *Bioorg. Med. Chem. Lett.* 12, 2829–2831

Magnesium lithospermate B and aldose reductase inhibition

Diabetes mellitus is the only non-infectious disease that is designated as an epidemic by the World Health Organization (http://www.who.int/en/). It is often accompanied by several long-term complications, namely neuropathy, nephropathy, retinopathy and cataract, whose occurrence has been linked to the modification of the physiological levels of glucose [6].

Although several drugs are available as antidiabetics, there are few drugs for the treatment of diabetic complications. They include salvianoric acid A [7] and several diterpenoids isolated from

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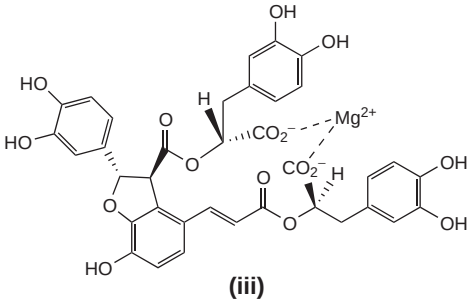
Salviae miltiorrhiza [8]. These have been reported to have aldose reductase (AR) inhibitory activity. The enzyme, which converts glucose to sorbitol, might be involved with another signal transduction process in the pathogenesis of diabetic nephropathy [9]. Jung and collaborators have recently reported [10] their study on magnesium lithospermate B (compound **iii**), whose vasodilating and antihypertensive effects have been previously reported [11]. In particular, they investigated the ability of magnesium lithospermate B to inhibit aldose reductase, and verified that such inhibition correlated with the production of fibronectin, which is responsible for the development of diabetic nephropathy.



(iii)

To this aim, mouse mesangial cells were treated for 24 hours with magnesium lithospermate B. Aldose reductase activity was then evaluated in the cell lysate by UV spectrometry and the amount of fibronectin was determined in the medium by western blot. Magnesium lithospermate B showed significant inhibition of AR (IC_{50} = 0.04 μM), being 2.5-fold more potent in this assay than epalrestat, a well-known inhibitor of AR (IC_{50} = 0.1 μM). The production of fibronectin was also significantly lower and showed a similar pattern as AR inhibition. Both sodium and barium lithospermate B showed similar behaviour in the two assays as magnesium lithospermate B. On the contrary, lithospermic acid B was a much weaker inhibitor of aldose reductase (IC_{50} = 12.16 μM).

6 Nuss, J.M. *et al.* (2000) In *Annual Reports in Medicinal Chemistry* (Vol. 35) (Doherty, A.M. ed.), pp. 211–220, Academic Press, London
7 Du, G-H. *et al.* (1995) Prevention of galactose-induced cataractogenesis in rats by salvianolic acid A. *Acta Pharm. Sin.* 30, 561–566
8 Tezuka, Y. *et al.* (1997) Aldose reductase inhibitory constituents of the root of Salvia miltiorhiza Bunge. *Chem. Pharm. Bull.* 45, 1306–1311
9 Shah, V.O. *et al.* (1997) Aldose reductase gene expression is increased in diabetic nephropathy. *J. Clin. Endocrinol. Metab.* 82, 2294–2298
10 Jung, M. *et al.* (2002) Effective isolation of magnesium lithospermate B and its inhibition of aldose reductase and fibronectin on mesangial cell line. *Chem. Pharm. Bull.* 50, 1135–1136
11 Yokozawa, T. *et al.* (1992) Effect of magnesium lithospermate B in rats with sodium-induced hypertension and renal failure. *Nephron* 60, 460–465

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Details of recent papers or those *in press* should be directed to Dr Steve Carney, Editor, *Drug Discovery Today*, Elsevier Science London, 84 Theobald's Road, London, UK WC1X 8RR. tel: +44 207 611 4132, fax: +44 207 611 4485, e-mail: s.carney@elsevier.com

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