

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.

Monitor Editor: Debbie Tranter

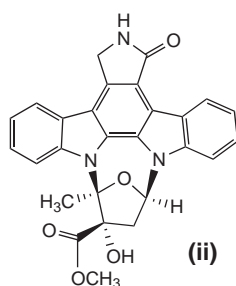
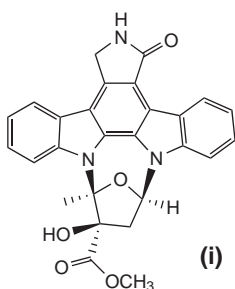
Monitor Authors:

Daniela Barlocco, *University of Milan*
David Barrett, *Fujisawa Pharmaceutical Company*
Paul Edwards, *Pfizer*
Steven Langston, *Millennium Pharmaceuticals*
Michael Walker, *Bristol-Myers Squibb*
John Weidner, *Emisphere*
Andrew Westwell, *Nottingham University*

Molecules

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

Compound (+)K252a (i), originally isolated from the culture broth of *Nocardiosis* 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.



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