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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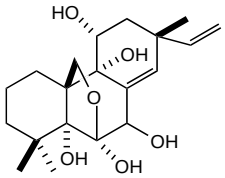
Molecules

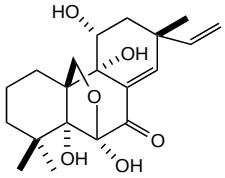
Novel antimycobacterial agents from the fungus *Diaporthe* Sp.

The incidence of tuberculosis infection has increased rapidly and multidrug resistant strains of *Mycobacterium tuberculosis* have emerged [1]. Therefore, the search for new drugs is of great importance. Dettrakul and collaborators [2] have reported the characterization of two new antitubercular pimarane diterpenes, diaporthein A (**i**) and diaporthein B (**ii**), from the culture broth of the fungus *Diaporthe* sp. BCC 6140. The structures of these compounds were determined from spectroscopic data. However, the stereochemistry at the C-7 of **i** could not be established from the available data and was tentatively defined as β by comparison with structurally related sphaeropsidins [3].

Compounds **i** and **ii** were tested for their antimycobacterial activity against *M.tuberculosis* H37Ra [4]. The antimycobacterial drugs Isoniazid [minimum inhibitory concentration (MIC) = 0.04–0.09 μg ml^{-1}] and kanamycin sulfate (MIC = 2.0–5.0 μg ml^{-1}) were used as reference drugs. In addition, the cytotoxicity of compounds **i** and **ii** was determined according to the colorimetric assay described by Skehan and co-workers [5]. The results indicated that diaporthein A has only weak antimycobacterial activity (MIC = 200 μg ml^{-1}). By contrast,



(i)



(ii)

diaporthein B is a potent inhibitor of *M. tuberculosis* growth (MIC = 3.1 μg ml^{-1}). Because the only difference between compound **i** and **ii** is the C-7 substituent, it can be assumed that the carbonyl moiety of diaporthein B is essential for the antimycobacterial activity of these compounds.

When compounds **i** and **ii** were tested for cytotoxicity in Vero cell lines, a trend similar to their antitubercular activity was seen (IC_{50} values >50 μg ml^{-1} and 1.5 μg ml^{-1}, respectively).

These compounds, therefore, have potential as novel antitubercular compounds that might be active against the numerous multidrug resistant strains of *M.tuberculosis*.

1 Bradford, W.Z. *et al.* (1996) The changing epidemiology of acquired drug-resistant tuberculosis in San Francisco. *Lancet*, 348, 928–931
2 Dettrakul, S. *et al.* (2003) Antimycobacterial pimarane diterpenes from the fungus *Diaporthe* Sp. *Biorg. Med. Chem. Lett.* 13, 1253–1255
3 Evidente, A. *et al.* (2002) Sphaeropsidins D and E, two other pimarane diterpenes, produced *in vitro* by the plant pathogenic fungus *Sphaeropsis sapinea* f. sp. *cupressi*. *Phytochemistry*, 59, 817–823
4 Collins, L. *et al.* (1997) Microplate alamar blue assay versus BACTEC 460 system for high-throughput screening of compounds against *Mycobacterium tuberculosis* and *Mycobacterium avium*. *Antimicrob. Agents Chemother.* 41, 1004–1009
5 Skehan, P. *et al.* (1990) New colorimetric cytotoxicity assay for anticancer-drug screening. *J. Natl. Cancer Inst.* 82, 1107–1112

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Novel antiviral molecules

Inhibitors of HIV-1 nuclear import

Translocation of transcribed viral DNA from the cytosol into the nucleus of an infected cell is required for HIV replication in non-dividing cells. HIV viral DNA is contained in a large complex of proteins referred to as the pre-integration complex (PIC), which includes integrase, reverse transcriptase, viral protein R and the matrix antigen (MA). There are two stretches of amino acids within the MA that are