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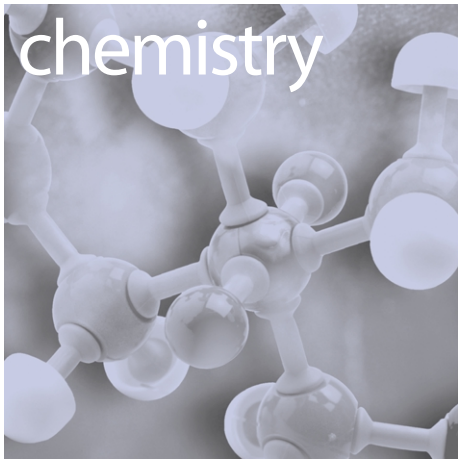
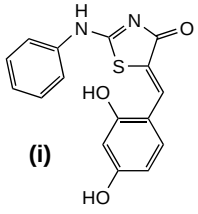


NOVEL ANTITUMOUR AGENTS

Selective induction of apoptosis in human colon cancer cells

Colorectal cancer is one of the leading causes of cancer-related mortality worldwide and currently available chemotherapeutic agents, administered alone or in combination, are frequently compromised by the development of drug resistance or by dose-limiting toxicities [1]. Hence, there exists an urgent requirement for new therapeutic agents to treat colorectal cancer with improved efficacy and tolerability.

Teraishi and co-workers (MD Anderson Cancer Center, University of Texas, Houston, TX, USA) have screened a chemical library (10,000 compounds), testing for cytotoxic effects in a range of human cancer cell lines [2]. This cell-based screen led to the identification of a new synthetic lead compound, DBPT **(i)**, with selective cytotoxic effects in human colon cancer cell lines [low μM IC_{50} values versus cancer cell lines DLD-1, HCT116 (p53-positive) and HCT116 (p53-negative)] compared with the less sensitive, normal human fibroblast cells.



(i)

Growth inhibition of colorectal cancer cells was found to be irrespective of p53 and P-glycoprotein status. The induction of apoptosis in DLD-1 cancer cells following treatment with DBPT was partially blocked by the general caspase inhibitor, benzyloxycarbonyl-valine-alanine-aspartate-fluoromethylketone. One particularly interesting aspect of this study concerns the role of c-Jun NH_2-terminal kinase (JNK), a member of the mitogen-activated protein kinase family, in mediating the apoptotic response to DBPT. Blocking JNK activation, using either a specific JNK inhibitor or a dominant-negative JNK gene, leads to abrogation of apoptosis in DLD-1 cells treated with DBPT. However, constitutive JNK activation alone did not reproduce the effects of DBPT and, overall, the apoptosis data suggested that DBPT induces apoptosis in colon cancer cell lines via caspase-dependent and caspase-independent pathways. DBPT, therefore, serves as an interesting lead for the development of new therapeutic agents that are active against colon cancer.

1 Iqbal, S. and Lenz, H. J. (2004) Integration of novel agents in the treatment of colorectal cancer. *Cancer Chemother. Pharmacol.* 54, 32–39.
2 Teraishi, F. *et al.* (2005) Identification of a novel synthetic thiazolidin compound capable of inducing c-Jun NH2-terminal kinase-dependent apoptosis in human colon cancer cells. *Cancer Res.* 65, 6380–6387.

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