and routine medicinal chemistry was used in the discovery of more potent farnesyltransferase inhibitors that inhibited Ras processing in whole cells.

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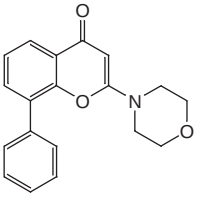
Molecular cancer target: PI-3-kinase

Many endogenous growth factors and oncogenes use the ubiquitous phosphoinositide (PI) signalling pathway for inducing proliferation of their target cells. This primary cellular communication pathway has thus become a favorite therapeutic target for the treatment of cancer. The simplest way to interfere with PI signalling involves inhibition of phosphatidylinositol-specific phospholipase C (PI-PLC), which hydrolyses membrane phosphatidylinositol-4,5-diphosphate [$PI(4,5)P_2$], generating two intracellular signalling molecules: inositol-1,4,5-triphosphate (IP_3) and diacylglycerol. The first regulates intracellular calcium ion levels and the second activates protein kinase C, which regulaties several cellular events. Consequently, PI-PLC inhibitors are also toxic to non-proliferating cells, as many other cellular functions, besides mitogenesis, utilize this signalling path.

Targeting phosphatidylinositol-3-kinase

An attractive cancer drug target is phosphatidylinositol-3-kinase (PI-3-kinase) that phosphorylates PI to generate phosphatidylinositol-3-phosphate [PI(3)P], which is further phosphorylated to $PI(3,4)P_2$ and $PI(3,4,5)P_3$. These membrane phospholipids participate in acute cellular responses activated by growth factors and oncogenes. Hence, reducing their cell membrane levels by inhibition of PI-3-kinase should in theory affect cancer cells more than nonmalignant cells. Indeed, both the fungal metabolite wortmannin and the natural bioflavinoid quercetin (known inhibitors of PI-3-kinase) exhibit potent antitumour activities *in vivo*. Unfortunately, these nonselective drugs also inhibit other kinases, resulting in toxicity towards nonmalignant cells. Lilly Research Laboratories have introduced the quercetin-like chromone, **1** [LY294002; 2-(4-morpholinyl)-8-phenyl-4*H*-1-benzopyran-4-one], as a selective and potent (IC_{50} = 1.4 μM) PI-3-kinase inhibitor [Vlahos, C.J. *et al. J. Biol. Chem.* (1994) 269, 5241–5248]. Compound **1** induced apoptosis in Ramos-Burkitt lymphoma B cells, indicating a potential application in the treatment of B cell lymphomas [Curnock, A.P. and Knox, K.A. *Cell. Immunol.* (1998) 187, 77–87]. Yet, at higher concentrations, **1** inhibits adrenal cortex type II PI-4-kinase, required for normal adrenal function [Downing, G.J. *et al. Biochemistry* (1996) 35, 3587–3594]. This could indicate that the therapeutic window of **1** might be relatively small.



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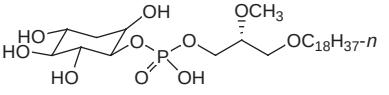
3-substituted myo-inositol derivatives

More recently Lixin Qiao and his colleagues of the Drug Discovery Program at Georgetown University Medical Center (Washington, DC, USA) and the Arizona Cancer Center (Tucson, AZ, USA) have described several 3-substituted myo-inositol derivatives that selectively inhibit PI-3-kinase. These inhibitors leave other aspects of the myo-inositol-signalling pathway intact, thereby limiting damage to non-malignant cells [Qiao, L. *et al. J. Med. Chem.* (1998) 41, 3303–3306]. However, such myo-inositol derivatives are sensitive to endogenous phospholipases, which minimizes their bioavailability. To overcome this problem, ether lipid analogues of 3-deoxy-PI were synthesized using 1-*O*-octadecyl-2-*O*-methyl-*sn*-glycerol. The resulting ether lipid 3-deoxy-PI analogue (**2**) potently inhibited bovine



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brain p110/p85 PI-3-kinase (IC_{50} = 2.5 μM), while concentrations tenfold higher inhibited bovine PI-PLC. This compound exhibited a similarly low IC_{50} value (2.1 μM) in a soft agarose colony formation assay using HT-29 human colon adenocarcinoma cells. This antitumour activity was also evident *in vivo*: HT-29 cells injected subcutaneously into immunodeficient *scid* mice formed solid tumours; but daily treatment with the ether lipid 3-deoxy-PI analogue **1** at 150 mg kg^{-1} i.p. reduced tumour volume by 67% ten days after inoculation. Thus, lipid analogues of 3-deoxy-PI are useful antitumour drug candidates with minimal toxicity towards normal cells. Moreover, their high lipophilicity allows good bioavailability and tumour penetration. Future designs of similar ether lipid analogues of 3-deoxy-PI should improve selectivity, further reducing inhibition of PI-PLC.

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