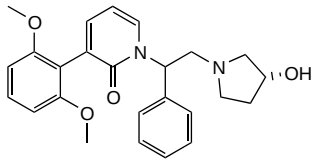
binding IC_{50} of 9.8 nM and >1000-fold selectivity over the delta opioid receptor and >390-fold selectivity over the mu opioid receptor. This work has generated rapid SAR in this KOR agonist series and further work in this area is warranted.



(iv)

2 Semple, G. *et. al* (2003) Synthesis and biological activity of kappa opioid receptor agonists. Part 2: preparation of 3-aryl-2-pyridine analogues generated by solution- and solid-phase parallel synthesis methods. *Bioorg. Med. Chem. Lett.* 13, 1141–1145

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Novel antitumour molecules

Antitumour vitamin analogues

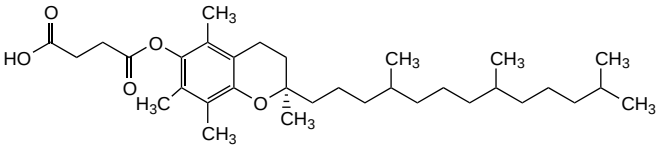
RRR-α-tocopheryl succinate [vitamin E succinate (VES), **i**], a hydrolysable ester derivative of RRR-α-tocopheryl (vitamin E, **ii**), is a potent growth inhibitor of a variety of human cancer cell lines and has been shown to have antitumour activity in animal xenograft and allograft models (i.p. administration). Previous studies have partially elucidated the mechanism of action associated with this agent; inhibition of cancer cell growth is a result of a concentration- and time-dependent inhibition of DNA synthesis and induction of cellular differentiation and apoptosis. A recent report by Yu and co-workers has further clarified the biochemical events involved in VES-induced apoptosis. These include: (1) the translocation of the pro-apoptotic protein Bax from the cytosol to the mitochondria and cytochrome c release from the mitochondria to the cytosol; (2) increased permeabilisation of mitochondrial membranes; and (3) the processing of caspase-9 and –3, but not caspase-8, into their active forms and cleavage of poly(ADP-ribose) polymerase (PARP) [1].

Lawson and co-workers have now reported the antitumour properties of a non-hydrolysable ether analogue of RRR-α-tocopherol, termed RRR-α-tocopherol ether-linked acetic acid analogue (α-TEA, **iii**) [2]. Analogue **iii** exhibited antitumour activity *in vitro* and *in vivo* using a syngeneic BALB/c mouse mammary tumour model. Similar to compound **i**, compound **iii** was capable of inducing apoptosis in human breast (MCF-7, MDA-MB-231, MDA-MB-435), ovarian (CP-70), cervical (ME-180), endometrial (RL-952), prostate (LnCaP, PC-3, DU-145), colon (HT-29, DLD-1), lung (A-549) and lymphoid (Raji, Ramos, Jurkat) cells.

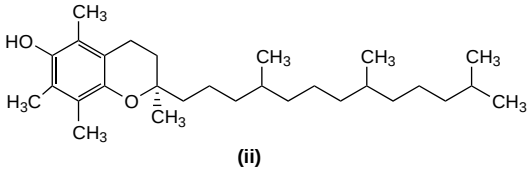
Because compound **iii** is a water-insoluble lipid, aerosol delivery of liposomal preparations was chosen as a potentially effective, clinically relevant method of delivery, a strategy previously shown to increase drug concentrations and effectiveness in the lungs and other organs compared with i.m. injection in mice. Mice treated with **iii** showed a significant decrease in tumour volumes and a reduction of lung metastases over 17 days of aerosol treatment.

A recent review article by Verrax and colleagues has detailed studies on the association of vitamins C and K_3 as a potential non-toxic adjuvant cancer therapy [3]. A deficiency of DNAse activity is a hallmark of cancer cells. These enzymes are reactivated at early stages of cancer cell death by vitamin C (acid DNase) and vitamin K_3 (alkaline DNase), which are themselves known to be cytotoxic in a number of cancer cell lines. Interestingly, co-administration of these vitamins (in a ratio of 100:1, for C and K_3 respectively) produced the following antitumour effects: (1) inhibition of cancer growth in transplantable liver tumour-bearing mice with a resulting increase in life span of 46%; (2) selective potentiation of cyclophosphamide chemotherapy; (3) sensitisation of tumours resistant to some drugs; and (4) potentiation of the effects of radiotherapy in mice. Morphological studies have shown that cell death occurs by autoschizis, a new type of cancer cell death that is characterised by the formation of H_2O_2 during vitamin redox cycling, oxidative stress, DNA fragmentation, no caspase-3 activation and cell membrane injury with progressive loss of organelle-free cytoplasm.

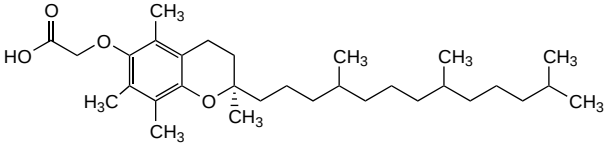
1 Yu, W. *et al.* (2003) RRR-α-tocopheryl succinate-induced apoptosis of human breast cancer cells involves Bax translocation to mitochondria. *Cancer Res.* 63, 2483–2491
2 Lawson, K.A. *et al.* (2003) Novel vitamin E analogues decreases syngeneic mouse mammary tumor burden and reduces lung metastasis. *Mol. Cancer Ther.* 2, 437–444
3 Verrax, J. *et al.* (2003) The association of vitamins C and K_3 kills cancer cells mainly by autoschizis, a novel form of cell death. Basis for their potential use as coadjuvants in anticancer therapy. *Eur. J. Med. Chem.* 38, 451–457



(i)



(ii)

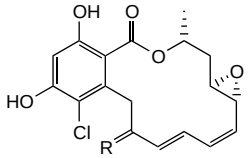


(iii)

 1359-6446/03/$ – see front matter PII: S1359-6446(03)02776-4

Novel derivatives of radicicol as antitumour agents

Radicicol (**iv**) is an antibiotic that was first isolated from the fungus *Monosporium bonorden* and was found to suppress cellular transformation by various oncogenes such as *src*, *ras*, *raf*, *mos* and *fos*. In addition, **iv** possessed potent *in vitro* anti-proliferative activity against a wide variety of human tumour cell lines, but was found to be inactive in *in vivo* antitumour models. The observation that the growth inhibitory effect of **iv** against v-src kinase was abolished by reducing agents such as dithiothreitol led to the development of novel oxime derivatives such as KF25706 (**v**) and KF29158 (**vi**), which are more stable than **iv** and show significant *in vivo* activities in human tumour xenograft models.



(iv) (R=O)
(v) (R=N-OH)
(vi) (R=N-OCH_2CONMe_2)
(vii) (R=N-OCH_2CO-piperidine)

One of the major intracellular targets of **iv** was revealed to be the heat-shock protein-90 (Hsp90) family, which play an essential role in the stability and function of a number of cellular proteins, including v-src, Raf-1, and epidermal growth factor receptor (EGFR). Hsp90 inhibitors result in the inhibition or degradation of these Hsp90-associated proteins, and might prove to have clinical benefit. Other Hsp90 inhibitors have also been reported and one of these, 17-allylamino-17-demethoxygeldanamycin, is currently in Phase 1 clinical trial. Ikuina and co-workers have recently reported the synthesis and antitumour evaluation of new *O*-carbamoylmethyloxime derivatives of **iv** against v-src- and K-Ras-transformed cells and for inhibitory activity against v-src tyrosine kinase [4]. Most notably, derivative **vii** exhibited a more potent antiproliferative activity than **iv** or **v** in 3Y1-B (normal rat fibroblast), SR-3Y1 (v-src-transformed), NRK (normal rat kidney epithelial) and KNRK5.2 (K-Ras-transformed) cell lines, with an IC_{50} value of 25 nM for the inhibition of v-src kinase activity. In addition, **vii** was found to possess significant *in vivo* activity in murine MX-1 and A431 xenografts.

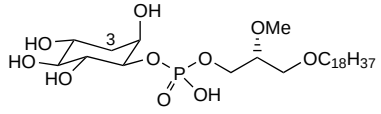
4 Ikuina, Y. *et al.* (2003) Synthesis and antitumor activity of novel *O*-carbamoylmethyloxime derivatives of radicicol. *J. Med. Chem.* 46, 2534–2541

D-3-Deoxy-phosphatidyl-*myo*-inositol analogues as novel growth inhibitory agents

The Ser/Thr protein kinase Akt (also known as protein kinase B) is a downstream target of PI-3 kinase, whose major role in cancer cell growth is in the survival signalling that is mediated by Akt to prevent apoptosis. PI-3 kinase phosphorylates the D-3-hydroxyl position of the *myo*-inositol ring of phosphatidylinositol (PtdIns). The PtdIns-3-phosphates subsequently bind to the pleckstrin homology (PH) domain of Akt, causing the translocation of Akt from the cytoplasm to the plasma membrane. Phosphorylation of Akt by phosphatidylinositol-dependent kinase-1 (PDK-1) then causes the detachment of Akt from the plasma membrane and its subsequent relocation to the nucleus, where activated Akt phosphorylates proteins such as Bad (an apoptosis inhibitor), FRAP (an activator of $p70^{S6k}$, which is required for cell cycle progression), caspase-9, forkhead transcription factors and nuclear factor kappa B (NF-κB). Through this mechanism, Akt regulates cell proliferation and promotes cell survival.

Activation of Akt is negatively regulated by the tumour suppressor protein PTEN/MMAC, a dual specificity tyrosine–threonine/lipid phosphatase that dephosphorylates the 3-position of PtdIns-3-phosphate, thereby inhibiting the PI-3 kinase/Akt signalling pathway. Somatic mutations of PTEN have been reported in several types of human tumours. Inhibition of Akt signalling therefore provides an opportunity to both inhibit a major survival pathway and replace the loss in activity of the tumour suppressor protein PTEN.

Meuillet and co-workers have reported a novel strategy to inhibit Akt activation through the use of D-3-deoxy-phosphatidyl-*myo*-inositols (DPIs) that cannot be phosphoylated in the usual 3-position of the *myo*-inositol ring [5]. In platelet-derived growth factor-stimulated mouse NIH3T3 cells, the three novel DPIs were shown to bind to the PH domain of Akt, trapping it in the cytoplasm and preventing Akt activation. D-3-Deoxy-phosphatidyl-myo-inositol-1-[(R)-2-methoxy-3-octadecyloxypropyl hydrogen phosphate] (DPIEL, **viii**) was the most active compound, preventing Akt translocation to the plasma membrane, but having no effect on myristylated Akt, a constitutively activated membrane-bound Akt expressed in NIH3T3 cells. Molecular modelling and docking studies show that DPIEL binds with high affinity to the PH domain of Akt. DPIs therefore represent a new class of potential anticancer drugs with a novel mechanism of action.



(viii)

5 Meuillet, E.J. *et al.* (2003) Specific inhibition of the Akt1 pleckstrin homology domain by D-3-deoxy-phosphatidyl-*myo*-inositol analogues. *Mol. Cancer Ther.* 2, 389–399

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