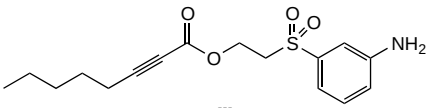
Monitor: molecules and profiles

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.

Molecules

VCAM-1 expression

Leukocyte recruitment into inflamed tissue is an essential physiological process that removes inflammatory stimuli. However, this response itself can lead to a chronic and detrimental inflammatory process if the stimuli are not properly eliminated. Thus, leukocyte recruitment itself is a key factor in the pathogenic process of inflammation. At the sites of inflammation the recruitment of leukocytes is mediated, in part, by the expression on endothelial cells of adhesion molecules, including vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1) and E-selectin, that are induced in response to various cytokines such as tumour necrosis factor-α (TNF-α). Steroids and other anti-inflammatory drugs with broad spectrum activities are effective in treating numerous diseases and inflammatory conditions. However, the long-term use of these drugs often leads to unacceptable side-effects. Some leukocytes, including T cells, monocytes and eosinophils, constitutively express very late antigen-4 (VLA-4), the receptor of VCAM-1, and are key effector cells in various inflammatory disorders. Tissue samples from patients have also indicated that VCAM-1 is highly expressed in many diseases. Selective inhibitors of VCAM-1 are therefore likely to have potential as therapeutic agents [1].



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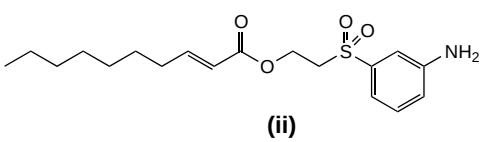

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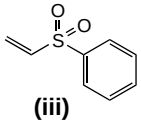

(iii)

A commercial library was screened giving rise to two hits, **i** and **ii**, which were weak inhibitors of inducible VCAM-1 expression. Subsequent optimisation improved the potency, leading to compound **iii**, which had an IC_{50} of 2 μM and was one of the most potent compounds synthesised. This work has indicated that α,β-unsaturated sulfones, discovered from a combinatorial library, are a new series of inhibitors of inducible VCAM-1 expression and the approach outlined here warrants further investigation to optimise this lead series still further.

1 Meng, C. Q. *et. Al.* (2003) Lead discovery of α,β-unsaturated sulfones from a combinatorial library as inhibitors of inducible VCAM-1 expression. *Bioorg. Med. Chem. Lett.*, 13, 745–748

Kappa opioid receptor agonists

Non-peptide ligands of the kappa opioid receptor (KOR) have been known for many years. These KOR agonists were initially targeted towards various pain indications but preliminary clinical studies showed that they produced severe centrally-mediated side-effects such as diuresis, sedation and dysphoria. Consequently, KOR agonists were dropped from development. No selective KOR agonist compounds have yet reached the market.

A strategy has recently been described for the preparation of KOR agonists with more polar substituents introduced to the core template to reduce lipophilicity and increase polar surface area, thereby reducing the compounds ability to cross the blood–brain barrier. Such compounds might still act at peripherally located KORs and thus might be useful for the treatment of visceral pain while avoiding the well-documented side-effects of previous KOR agonists [2]. Several libraries were prepared, both in solution-phase and solid-phase (on Wang resin). From these libraries of purified single compounds, each compound isolated was screened against opioid receptors using classical filter binding assays that measured the displacement of the appropriate radiolabelled ligand from the membranes of HEK293 cells overexpressing the requisite human opioid receptor. One of the most potent compound isolated was **iv**, which possessed a kappa opioid

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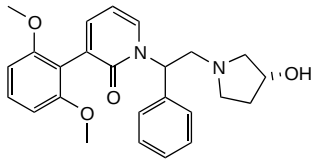
binding IC_{50} of 9.8 nM and >1000-fold selectivity over the delta opioid receptor and >390-fold selectivity over the mu opioid receptor. This work has generated rapid SAR in this KOR agonist series and further work in this area is warranted.



(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

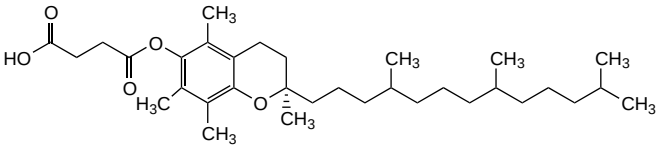
RRR-α-tocopheryl succinate [vitamin E succinate (VES), **i**], a hydrolysable ester derivative of RRR-α-tocopheryl (vitamin E, **ii**), is a potent growth inhibitor of a variety of human cancer cell lines and has been shown to have antitumour activity in animal xenograft and allograft models (i.p. administration). 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



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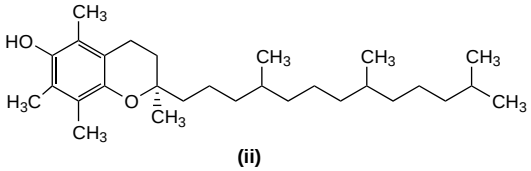

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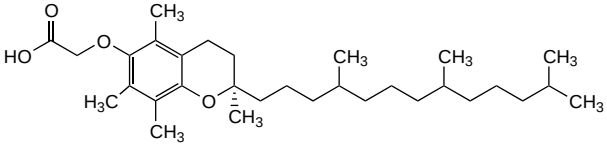

(iii)

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