Monitor

Monitor provides an insight into the latest developments in the pharmaceutical and biotechnology industries. ***Chemistry*** examines and summarises recent presentations and publications in medicinal chemistry in the form of expert overviews of their biological and chemical significance, while ***Profiles*** provides commentaries on promising lines of research, new molecular targets and technologies. ***Biology*** reports on new significant breakthroughs in the field of biology and their relevance to drug discovery. ***Business*** reports on the latest patents and collaborations, and ***People*** provides information on the most recent personnel changes within the drug discovery industry.

Chemistry

Molecules

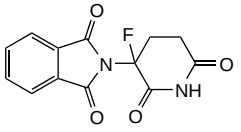
Thalidomide analogues as anti-inflammatory agents

Thalidomide was introduced on to the market in 1956 to treat morning sickness, ironically, because of its remarkable lack of toxicity. In addition, thalidomide was prescribed as a sedative because it was devoid of the toxicity associated with the then class of choice for sedation, the barbiturates. By 1962 however, it was thought to be responsible for more than 8000 birth defects.

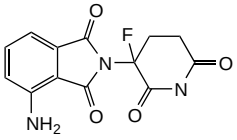
Interest in thalidomide was revived with the discovery of its immunomodulatory activity, leading to its use in the treatment of erythema nodosum leprosum (ENL), an inflammatory state that can occur in leprosy. Subsequent research suggested that this activity might be because of the ability of thalidomide to inhibit TNF-α [1]. More recently, thalidomide has been widely used in the treatment of multiple myeloma [2].

Thalidomide is a chiral molecule and it had been suggested that the teratogenic activity resided in the S-isomer. However, the validity of this statement was questionable owing to the insensitivity of the test species (mouse) [3] to the teratogenic effects of thalidomide and the chiral instability of the drug *in vitro* and *in vivo*.

In an interesting recent paper, Hon-Wah Man [4] reports on the synthesis of the chirally stable analogues of thalidomide, α-fluorothalidomide (**i**) and α-fluoro-4-aminothalidomide (**ii**), produced by substitution of fluorine for hydrogen by electrophilic fluorination at the asymmetric centre of the molecule.



(i)



(ii)

Compound **i** was cytotoxic in human peripheral blood mononuclear cells (hPBMCs) at a concentration of 100 μM, yet exhibited no ability to inhibit TNF-α at non-toxic concentrations (10 μM). However, compound **ii**, although less potent than the des-fluoroanalogue, was still 830-fold more potent than thalidomide. It did not exhibit cytotoxicity at any dose tested. Continuing research on the SAR of thalidomide analogues will hopefully yield potent, non-toxic agents of use in inflammatory diseases and cancer.

1 Sampaio, E.P. *et al.* (1991) Thalidomide selectively inhibits tumor necrosis factor alpha production by stimulated human monocytes. *J. Exp. Med.* 173, 699–703
2 Weber, D. (2003) Thalidomide and its derivatives: new promise for multiple myeloma. *Cancer Control* 10, 375–383
3 Winter, W. and Frankus, E. (1992) Thalidomide enantiomers. *The Lancet* 379, 365
4 Man, H.-W. (2003) α-Fluoro-substituted thalidomide analogues. *Bioorg. Med. Chem. Letts.* 13, 3415–3417

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Antitumour properties of a reversible methionine aminopeptidase-2 inhibitor

The discovery that the widely studied anticancer agent TNP-470 (**iii**), as well as its precursor fumagillin (**iv**), exhibited their antitumour properties through irreversible inhibition of the intracellular metalloenzyme methionine aminopeptidase-2 (MetAP2) [5] has prompted renewed interest in this enzyme as a target for anticancer drug design. TNP-470 proved efficacious in a range of preclinical xenograft models of human tumours, and cases of complete remission (metastatic cervical cancer), tumour regression (metastatic breast cancer), and stable disease (sarcoma, melanoma, and adenocarcinoma) have been reported. However, dose-limiting neurotoxicity associated with TNP-470 was also reported in clinical studies.

MetAP2 is one of only two MetAPs known to be present in eukaryotes and is

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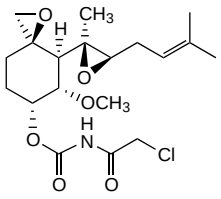
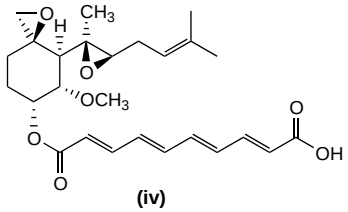


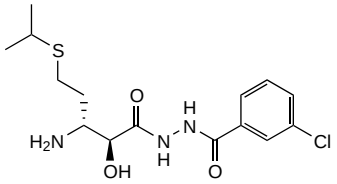
(iii)



(iv)

responsible for removing the NH_2-terminal initiator methionine residue from nascent proteins. MetAPs also play a role in protein cotranslational and/or post-translational modifications, and in maintaining protein stability. Notably, MetAP2 (but not MetAP1) is upregulated during cell proliferation, and inhibition of MetAP activity is thought to affect protein activity, subcellular localisation and degradation, leading to signal transduction and cell cycle interference.

TNP-470 irreversibly inhibits MetAP2 through formation of a covalent adduct (epoxide alkylation by an active site His231 residue), and might alkylate additional proteins, leading to the toxic side effects shown by this drug. Wang and co-workers have now reported a rationally designed (via analysis of enzyme-inhibitor complex crystal structure and parallel synthesis) reversible MetAP2 enzyme inhibitor (A-357300, **v**) with potent and selective MetAP2 inhibition ($IC_{50} = 0.12\ \mu M$) over MetAP1 inhibition ($IC_{50} = 57\ \mu M$) [6]. A-357300 selectively induces cytostasis by G_1 cell cycle arrest in endothelial cells and in a subset of tumour cells, but not in most primary cells of non-endothelial type. In addition, inhibition of angiogenesis (both *in vitro* and *in vivo*) and potent antitumour



(v)

efficacy in carcinoma, sarcoma and neuroblastoma murine models was observed, establishing that reversible MetAP2 inhibitors could have value as novel cancer therapeutic agents.

5 Griffith, E.C. *et al.* (1997) Methionine aminopeptidase (type 2) is the common target for angiogenesis inhibitors AGM-1470 and ovalicin. *Chem. Biol.* 4, 461–467

6 Wang, J. *et al.* (2003) Tumor suppression by a rationally designed reversible inhibitor of methionine aminopeptidase-2. *Cancer Res.* 63, 7861–7869

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Biology

Cancer biology

Chemical modulation of ER: a novel strategy for the treatment of breast cancer

Since the early 1970s, Tamoxifen has been widely prescribed for the treatment of breast cancer. This drug acts by competing with the natural ligand for binding to the estrogen receptor (ER), thereby modifying ER activity. However, Tamoxifen is only effective in tumours that retain ER expression and/or function and acquired drug resistance is a common occurrence. Thus, novel compounds are requried to circumvent this problem.

Wang *et al.* [1] have taken the innovative approach of targeting the ER DNA-binding domain. This region of the protein comprises two non-equivalent zinc finger motifs that act in concert to mediate ER dimerization and DNA binding. The authors proposed that disruption of the zinc fingers might perturb ER function. To test this hypothesis they analyzed the anti-ER activity of several electrophilic agents. The disulphide benzamine, DIBA, and the benzisothiazolone, BITA, inhibited estradiol stimulated proliferation of ER-positive, but not ER-negative, cell lines; however, other electrophilic agents were ineffective. Similar results were also observed *in vivo* when nude mice harbouring breast carcinoma xenografts were treated with the compounds. At the molecular level, gene analysis demonstrated reduced E2F and anti-apoptosis gene expression, with a concomitant increase in cell cycle inhibitory genes.

The results of this study are encouraging because they demonstrate that it is possible to selectively modulate ER function by disrupting the DNA-binding domain. This might prove a tenable alternative to targeting the ER ligand-binding domain, a strategy that has been associated with acquired drug resistance. Thus, although further work is required to evaluate selectivity, potency and toxicity, the use of electrophilic agents represents a novel approach for the treatment of ER-positive breast cancers.

1 Wang, L.H. *et al.* (2004) Suppression of breast cancer by chemical modulation of vulnerable zinc fingers in estrogen receptor. *Nat. Med.* 10, 40–47

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Function of *BLM* – the gene mutated in Bloom's syndrome

Mutations in a human gene, *BLM*, cause a rare genetic disorder known as Bloom's syndrome. This condition is typically characterized by increased genomic instability and cancer predisposition.

The *BLM* gene encodes a DNA helicase belonging to the evolutionarily conserved RecQ family of DNA helicases. BLM interacts with and stimulates the activity of hTOPIIIα, a type IA topoisomerase also implicated in homologous recombination that can catalyze the unlinking of DNA molecules. Wu and Hickson [2] investigated the ability of recombinant BLM and hTOPIIIα proteins to resolve a synthetic oligonucleotide resembling two DNA molecules intertwined into a

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