9 Yoshikawa, Y. *et al.* (2001) New insulinomimetic zinc(II) complexes of α-amino acids and their derivatives with $Zn(N_2O_2)$ coordination mode. *Chem. Pharm. Bull.* 49, 652–654
10 Smith, K.T. *et al.* (1988) *Trace Mineral in Foods*, p. 209, Marcel Dekker
11 Smith, K.T. *et al.* (1988) *Trace Mineral in Foods*, p. 257, Marcel Dekker
12 Yoshikawa, Y. *et al.* (2000) New insulin-mimetic zinc (II) complexes; *bis*-maltolato zinc (II) and *bis*-2-hydroxypyridine-*N*-oxido zinc (II) with $Zn(O_4)$ coordination mode. *Chem. Lett.* 874–875

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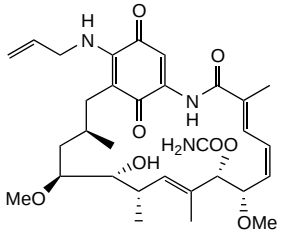
Novel antitumour molecules

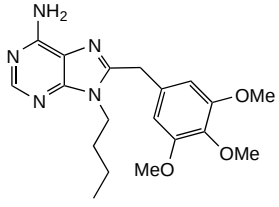
A small-molecule Hsp90 inhibitor inducing Her2 degradation

The Hsp90 (heat-shock protein) family of molecular chaperones play a key role in the ATP-dependent refolding of denatured proteins and the conformational maturation of a variety of key cell-signalling proteins that are frequently overexpressed in human cancers, including Raf and some tyrosine kinases (e.g. Met and Her2). In addition, Hsp90 is thought to play a role in maintaining the stability and function of mutated form of proteins such as p53 and *v*-src, but is required to a much lesser extent or not at all for their wildtype counterparts. Hsp90s have also been shown to be overexpressed in multiple tumour types, and cancer cells seem to be especially sensitive to Hsp90 inhibition. For these reasons, Hsp90 would appear to be an attractive target for anticancer therapeutic intervention.

The ansamycin antibiotics geldanamycin, herbimycin and radicicol have been found to cause Hsp90 inhibition by binding in the Hsp90 *N*-terminal ATP/ADP-binding pocket, and a synthetic analogue, 17-allylaminogeldanamycin **(i)** is currently in Phase I clinical trials as an Hsp90 inhibitor. However, **(i)** is relatively insoluble in formulatable solvents, is not easily synthesized and is unselective among the family of (at least four) Hsp90 family members. Chiosis and coworkers at the Memorial Sloan-Kettering Cancer Center (New York, NY, USA) have used the structural features of the Hsp90 binding pocket to design a small-molecule purine-derived Hsp90 inhibitor, PU3 **(ii)** (Ref. 1). This was found to bind competitively with geldanamycin for Hsp90 and induce protein degradation, including Her2, in a similar manner to geldanamycin. PU3 was also found to inhibit the growth of breast cancer cells, causing retinoblastoma protein hypophosphorylation, G1 arrest and differentiation, and thus could provide a new strategy for cancer treatment.



(i)

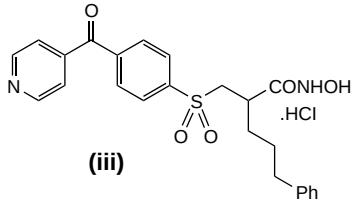


(ii)

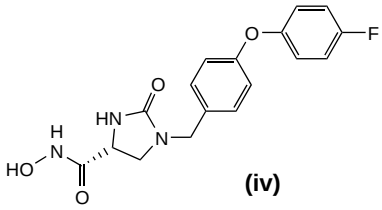
1 Chiosis, G. *et al.* (2001) A small molecule designed to bind to the adenine nucleotide pocket of Hsp90 causes Her2 degradation and the growth arrest and differentiation of breast cancer cells. *Chem. Biol.* 8, 289–299

Selective matrix metalloproteinase inhibitors

There is a well-established association between matrix metalloproteinase (MMP) overexpression and diseases such as metastatic cancer and arthritis. Despite intensive research efforts, the clinical development of MMP inhibitors (e.g. Marimastat) has been hampered by side effects such as musculoskeletal pain and stiffness (limiting the maximum tolerable dose), which are thought to arise at least in part from activity against the shedding of ectodomain proteins, or so-called 'sheddase' activity. Watson and coworkers at Celltech Chiroscience (Cambridge, UK) have used computer-aided molecular design techniques to search databases for non-peptidic selective inhibitors of MMP-8, based on the MMP-8 crystal structure[2]. Several modestly potent inhibitors were identified, from which chemical lead-optimization produced potent MMP-8 inhibitors, such as **(iii)**. Compound **(iii)** was found to inhibit MMP-8 with an IC_{50} value of 3 nM (together with MMP-2 and MMP-9 in the nanomolar range) when tested against a range of MMPs. Encouragingly, no activity against the shedding of ectodomain proteins was observed.



(iii)



(iv)

In related work, Robinson and coworkers at Pfizer Global Research and Development (Groton, CT, USA) have described the design, synthesis and evaluation of a series of imidazolidinone-based compounds as MMP-13 inhibitors[3]. The most notable finding amongst these was derivative **(iv)**, which selectively inhibited MMP-13 with an IC_{50} value of 3 nM.

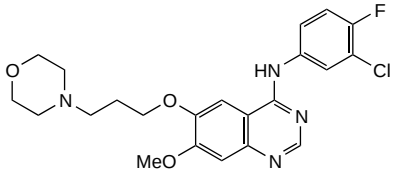
2 Baxter, A.D. *et al.* (2001) Arylsulphonyl hydroxamic acids: potent and selective matrix metalloproteinase inhibitors. *Bioorg. Med. Chem. Lett.* 11, 1465–1468

1359-6446/01/$ – see front matter PII: S1359-6446(01)01947-X

3 Robinson, R.P. *et al.* (2001) Design and synthesis of 2-oxo-imidazolidine-4-carboxylic acid hydroxyamides as potent matrix metalloproteinase-13 inhibitors. *Bioorg. Med. Chem. Lett.* 11, 1211–1213

Development of ZD1839 (Iressa™) – an orally active, selective epidermal growth-factor receptor tyrosine-kinase inhibitor

The use of 4-anilinoquinazolines for the inhibition of epidermal growth factor receptor tyrosine kinase activity in anti-cancer drug discovery is well-documented. Gibson and coworkers (AstraZeneca, Macclesfield, UK) have described the development of one such 4-anilinoquinazoline, ZD1839 (Iressa™) **(v)**, which is currently in advanced clinical development[4]. Factors such as the suppression of oxidative metabolism, inhibition of a broad range of human solid-tumour xenografts in a dose-dependent manner, good oral bioavailability and a long half-life in humans are described in the context of clinical candidate selection.

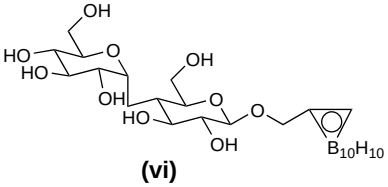


(v)

4 Barker, A.J. *et al.* (2001) Studies leading to the identification of ZD1839 (Iressa™): An orally active, selective epidermal growth factor receptor tyrosine kinase inhibitor targeted to the treatment of cancer. *Bioorg. Med. Chem. Lett.* 11, 1911–1914

Ortho-Carboranyl glycosides for the treatment of cancer by boron neutron-capture therapy

Boron neutron-capture therapy (BNCT) has been the subject of recent intensive research into cancer treatment. The therapy is based on the property of ^{10}B to react with slow neutrons to generate $^{7}Li^{3+}$ and $^{4}He^{2+}$ in a nuclear reaction, which can generate a strong cytotoxic effect, provided that a sufficient amount of boron (20–30 μg boron per g tissue) can be localized in the tumour tissue. Many previously reported compounds for this kind of therapy have been deemed unsuitable because of low water-solubility, low stability, high toxicity and/or low selectivity for tumour cells. Tietze and coworkers at Georg-August-Universität (Göttingen, Germany) have described the evaluation of the water-soluble and relatively non-toxic carboranyl glycosides [such as **(vi)**] for their suitability for BNCT as compared with the clinically used *para*-boronophenylalanine[5]. The boron uptake into B16-melanoma cells was significantly higher for compound **(vi)** (20.0 ppm after 24 h) than for *p*-boronophenylalanine (3.1 ppm after 24 h). The carboranyl maltoside **(vi)** was more effective than boron-10 enriched *p*-boronophenylalanine in killing C-6 rat glioma cells, by incubating the cells with compound followed by thermal neutron treatment. Compound **(vi)**, administered intravenously (25 mg of boron per kg in rats bearing brain tumours), gave a boron concentration of 3.0 ppm in the tumour tissue after a period of 4 h.

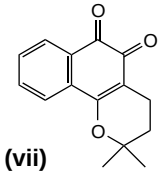


(vi)

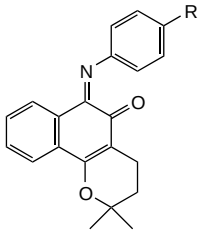
5 Tietze, L.F. *et al.* (2001) *Ortho*-Carboranyl glycosides for the treatment of cancer by boron neutron capture therapy. *Bioorg. Med. Chem.* 9, 1747–1752

Mono(arylimino) derivatives of the antitumour agent β-lapachone

β-Lapachone **(vii)**, found in the heartwood of the lapacho tree native to Central and South America, exhibits activity against various cancer cell lines *in vitro*, and at low doses is a radiosensitizer of several human cancer cell lines. *In vitro* effects include inhibition of topoisomerase I and the induction of topoisomerase IIα-mediated DNA strand breaks. In combination with taxol, β-lapachone is highly effective against human ovarian and prostate tumours implanted in immunosuppressed mice; however, its *in vivo* targets remain largely unknown. Recent evidence has supported participation of NAD(P)H:quinone oxidoreductase (NQ01) in the activation process, enhancing its cytotoxicity. Burton and coworkers (Universidad de Buenos Aires, Argentina) have reported the synthesis of monoarylimino *o*-quinones derived from β-lapachone that are intended to modify the centre of redox activity and alter the redox cycling characteristics of the parent molecule[6]. The phenylimine or *p*-methylphenylimine derivatives **(viii)** were found to retain (or better) most of the cytotoxicity and selectivity of the parent quinone when tested *in vitro* in the National Cancer Institute (NCI, Bethesda, MD, USA) screen (55 cancer cell lines). In preliminary *in vivo* testing using the NCI hollow-fibre assay compounds **(viii)** caused net cell-kills (reduction of the viable tumour cell-mass), whereas β-lapachone **(vii)** did not.



(vii)



(viii)
(R = H, Me)

6 Di Chenna, P.H. *et al.* (2001) Preparation and cytotoxicity toward cancer cells of mono(arylimino) derivatives of β-lapachone. *J. Med. Chem.* 44, 2486–2489

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