monitor

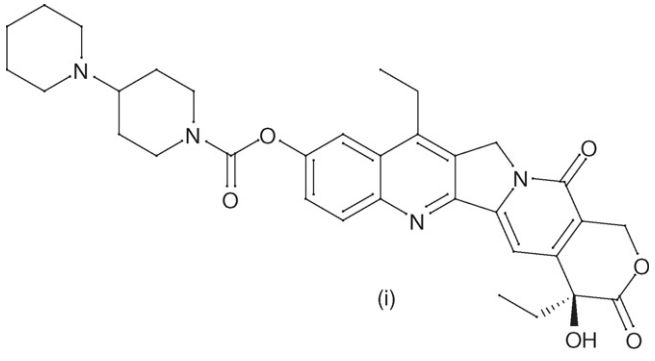
MOLECULES

Novel antitumour agents

A highly active and stabilized antitumour nanoliposomal irinotecan

Liposome-based constructs have demonstrated the ability to enhance efficacy and reduce systemic toxicity for certain anticancer drugs [1]. Nanoparticle systems can be engineered for stable encapsulation of the drug compound within the liposome, leading to long circulation times and accumulation at sites of cancer, followed by intratumoural drug release. This concept has been successfully applied, for example, for the anthracycline class of anticancer agents, and PEGylated liposomal doxorubicin [2] has received FDA approval for the treatment of cancer. The success achieved with liposomal–anthracycline systems has generally not been replicated for other classes of anticancer agents, although progress has been made with vincristine and some camptothecin analogues. The difficulty in stably encapsulating agents in the liposome interior, using remote-loading methodologies to give stable liposome formulations, is a key reason for the relative lack of success with other agent classes.

Drummond and co-workers have now reported a new nanoparticle–liposomal construct of the clinically used camptothecin prodrug CPT-11 (irinotecan; **i**) [3]. The system features a sterically hindered amine (triethylammonium) with highly charged, multivalent anionic trapping agents, either nonpolymeric (sucrose octasulfate) or polymeric (polyphosphate), as intraliposomal trapping agents. Liposomal entrapment of the resulting nanoscale complex gave extremely high drug:lipid ratios (>800 g CPT-11/mol phospholipid). Importantly, encapsulated drug remained in *in vivo* circulation for long periods (half-life for drug release = 56.8 h) and the system was protected from hydrolysis to the inactive carboxylate form and from metabolic esterase conversion. Nanoliposomal CPT-11 demonstrated markedly superior efficacy in human breast (BT474) and colon (HT29) cancer xenograft models compared with free CPT-11, and a substantially higher maximum tolerated dose in normal mice (>320 mg/kg compared with 80 mg/kg for free CPT-11). A related paper from the same group has described the local administration of nanoliposomal CPT-11 to brain tumours using convection-enhanced delivery, resulting in similar improvements in efficacy and host toxicity [4]. The demonstration of marked *in vivo* activity combined with low toxicity for this type of system represents an important step forward.



(i)

Orally active heat shock protein 90 inhibitors

The molecular chaperone known as heat shock protein 90 (Hsp90) is a very promising anticancer drug target. The main role of Hsp90 is to maintain 'client' proteins in their proper conformation [5], and Hsp90 inhibition has been shown to produce aberrantly folded proteins that are subsequently subjected to ubiquitination and proteosomal destruction. Fortuitously, from a drug discovery perspective, the Hsp90 client protein list contains several notorious oncogenes, including clinically validated targets (such as HER-2/neu, Bcr–Abl, the oestrogen receptor and the androgen receptor), growth signalling proteins and proteins involved in apoptosis evasion, cellular immortality, angiogenesis and metastasis. The simultaneous depletion of multiple oncogenic proteins by Hsp90 inhibition (reducing the likelihood for the development of resistance pathways) is potentially a very powerful weapon against cancer.

The natural product geldanamycin (**iia**) and its semisynthetic derivatives (**iib,iic**) are potent Hsp90 inhibitors [6] that have been studied in clinical trials, but suffer pharmaceutical drawbacks in terms of expensive manufacture and formulation difficulties. In addition, geldanamycin analogues are presently administered parenterally, prompting the search for structurally simple, orally active Hsp90 inhibitors.

Several synthetic Hsp90 inhibitors, such as the 8-benzyladenine derivative PU24FCl (**iii**), have been reported [7], but none as yet are suitable for oral administration. Biamonte and co-workers [8] have now reported that water solubility and oral bioavailability can be achieved by the insertion of an amino functionality in the N(9)

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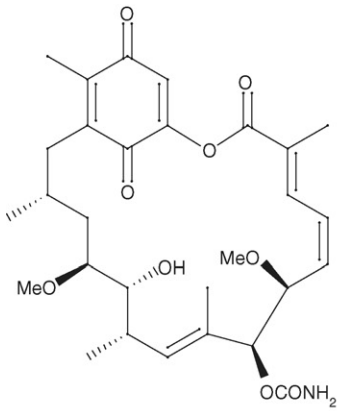
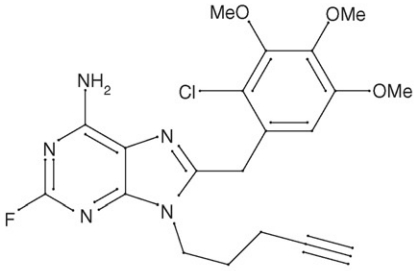
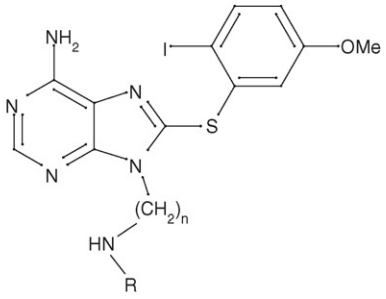


(ii a) R = OMe
(ii b) R = NHAllyl
(ii c) R = $NH(CH_2)_2NMe_2$



(iii) PU24FCl



(iv a) n=2, R=CH_2tBu
(iv b) n=3, R=CHMeEt
(iv c) n=3, R=*i*Pr

side chain of 8-sulfanyladenines. Using the established and highly reproducible HER-2 assay (monitoring the degradation of HER-2, an Hsp90 client protein), compound (**iva)** emerged as the most potent among the series of analogues (HER-2 IC_{50} = 90 nM). When administered orally at 200 mg/kg, the H_3PO_4 salts of compounds (**iva–c)** induced tumour growth inhibition in a murine xenograft model (gastric N87). Further preclinical data on orally active Hsp90 inhibitors will help to generate interest in this class of agent as potential anticancer agents of the future.

1 Allen, T.M. and Cullis, P.R. (2004) Drug delivery systems: entering the mainstream. *Science* 303, 1818–1822
2 Gabizon, A. *et al.* (1994) Prolonged circulation time and enhanced accumulation in malignant exudates of doxorubicin encapsulated in polyethylene-glycol coated liposomes. *Cancer Res.* 54, 987–992
3 Drummond, D.C. *et al.* (2006) Development of a highly active nanoliposomal irinotecan using a novel intraliposomal stabilization strategy. *Cancer Res.* 66, 3271–3277
4 Noble, C.O. *et al.* (2006) Novel liposomal CPT-11 infused by convection-enhanced delivery in intracranial tumors: pharmacology and efficacy. *Cancer Res.* 66, 2801–2808
5 Kamal, A. *et al.* (2004) Therapeutic and diagnostic implications of Hsp90 activation. *Trends Mol. Med.* 10, 283–290
6 Kamal, A. *et al.* (2003) A high-affinity conformation of Hsp90 confers tumour selectivity on Hsp90 inhibitors. *Nature* 425, 407–410
7 Vilenchik, M. *et al.* (2004) Targeting wide-range oncogenic transformation via PU24FCl, a specific inhibitor of tumor Hsp90. *Chem. Biol.* 11, 787–797
8 Biamonte, M.A. *et al.* (2006) Orally active purine-based inhibitors of the heat shock protein 90. *J. Med. Chem.* 49, 817–828

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