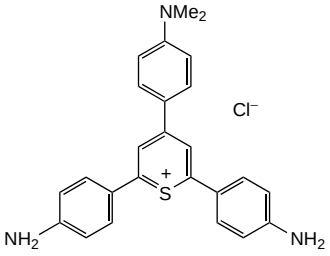
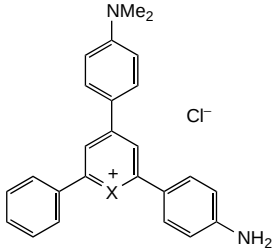
materials as sensitizers for use in PDT. In addition, various classes of cationic dyes have been explored as sensitizers. These materials typically have absorption maxima values of >600 nm and have molar extinction coefficients of $\geq 10^4$ M cm^{-1}, which make them more effective than Photofrin® and other porphyrin-derived sensitizers[7]. The compound 2,6-*bis*(4-aminophenyl)-4-(dimethylaminophenyl) thiopyrylium chloride [AA1,**(vi)**], selectively accumulates in tumours, but it has an absorption maxima value of <600 nm and low quantum yield for the generation of singlet oxygen [$\Phi(^1O_2) = <0.01$], which is a cytotoxic species generated by irradiation of the sensitizer.



(vi)

On the basis of their previous results in this field, Detty and coworkers have recently reported[8] a series of chalcogenopyrylium dyes [**(vii)–(ix)**], structurally related to **(vi)**. In particular, compound **(viii)** (X = Se), when tested *in vivo* against R3230AC mammary adenocarcinomas in female Fischer rats, demonstrated a 300% increase in tumour-doubling time compared with untreated control animals.



(vii) X = S
(viii) X = Se
(ix) X = Te

Furthermore, because of its relatively low log-P value (0.8), no skin photosensitivity was observed in treated animals. The authors suggest that the singlet-oxygen-induced damage to mitochondria [$\Phi(^1O_2) = 0.029 \pm 0.005$ in methanol], is a possible mechanism of action.

Novel derivatives of this class, which retain one anilino substituent and one 4-dimethylanilino substituent while the third substituent is varied, are being studied with the aim of optimizing their properties for PDT.

7 Dougherty, T.J. *et al.* (1998) Photodynamic therapy. *J. Natl. Cancer Inst.* 90, 889–905

8 Detty, M.R. *et al.* (2000) A selenopyrylium photosensitizer for photodynamic therapy related in structure to the antitumor agent AA1 with potent *in vivo* activity and no long-term skin photosensitization. *J. Med. Chem.* 43, 4488–4498

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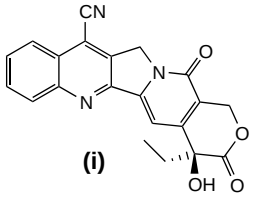
Novel antitumour molecules

Novel substituted camptothecins with potent antitumour activity

Inhibition of the enzyme DNA topoisomerase I, which is essential for the relaxation of DNA structure during several crucial cellular processes, has proven to be an attractive strategy in anticancer drug design. Two drugs in this class, Camptosar® (CPT11) and Hycamtin® (topotecan), which are related to the alkaloid camptothecin, have received FDA approval for use in the treatment of certain types of solid tumours, and intensive efforts to find new topo-I inhibitors are continuing. Two reports of new camptothecin analogues with potent anticancer activity have recently been described that have focused on analogues with differing substituents in the A/B rings, which modelling studies have suggested would optimize inhibition. Merlini and coworkers have reported the synthesis and evaluation of new camptothecins substituted in position 7 with alkyl or alkenyl chains bearing cyano and/or carboethoxy groups[1]. Most notably, the 7-cyano-camptothecin analogue **(i)** demonstrated high *in vitro* cytotoxicity against a topotecan-resistant H460 (non-small-cell lung cancer) cell line and a cisplatin-resistant ovarian carcinoma cell line. *In vivo* evaluation indicated that **(i)** was more cytotoxic than topotecan in the H460 tumour model, and was comparable with topotecan in both a small-cell lung carcinoma model and a colon carcinoma model; hence, further preclinical evaluation of this compound would be desirable.



(i)

Because camptothecins contain an α-hydroxy-δ-lactone they exist in two distinct forms at physiological pH: a biologically active 'lactone-closed' form and a biologically inactive 'lactone-opened' form. Hydrolysis to generate the lactone-opened form inactivates the parent drug, a problem that is exacerbated in human blood because the abundant blood-serum protein, albumin, preferentially binds to this form. Establishing the physiological conditions required to achieve a therapeutically relevant concentration of the lactone-closed form in tumour cells, therefore, is a major challenge in this field. This has been addressed by Burke and coworkers, who have described a novel silatecan **(ii)**, which has a closed lactone ring and displays high lipophilicity, improved human blood stability and potent anticancer activity[2]. The combination of its potency and stability profiles suggests that **(ii)** could be more efficacious than the currently used camptothecin-based therapies.

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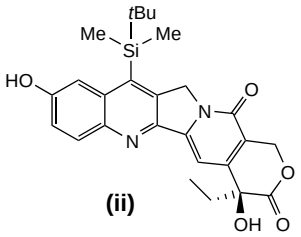


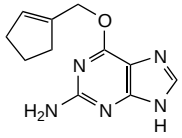
(ii)

1 Merlini, L. *et al.* (2000) Novel 7-substituted camptothecins with potent antitumor activity. *J. Med. Chem.* 43, 3963–3969

2 Burke, T.G. *et al.* (2000) The novel silatecan 7-*tert*-butyldimethylsilyl-10-hydroxycamptothecin displays high lipophilicity, improved human blood stability, and potent anticancer activity. *J. Med. Chem.* 43, 3970–3980

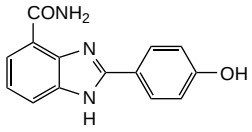
DNA-repair inhibitors for enhancing cancer therapies

The DNA repair enzyme *O*^{6}-alkylguanine-DNA alkyltransferase (AGT) repairs *O*^{6}-alkylguanine lesions, following exposure to alkylating agents, by the irreversible and stoichiometric transferral of the *O*^{6}-alkyl group to a cysteine thiolate in the active site of the enzyme. Because high levels of AGT have been shown to confer resistance to anticancer alkylating agents, inactivation and depletion of AGT potentiates the cytotoxicity of chemotherapeutic agents that function via guanine *O*^{6}-alkylation. Several point mutations in the human sequence that render AGT resistant to inactivation by the AGT inhibitor, *O*^{6}-benzylguanine (BG), have been reported. The development of additional inhibitors that are able to inactivate these resistant mutants is, therefore, desirable. Griffin and coworkers have synthesized and evaluated a series of *O*^{6}-allyl and *O*^{6}-(2-oxoalkyl) guanines as potential AGT inhibitors[3] and compared them with corresponding *O*^{6}-alkylguanines. *O*^{6}-cycloalkenylguanines proved to be the most potent AGT inhibitors studied, and 1-cyclopentenylmethylguanine **(iii)** was found to enhance the *in vitro* cytotoxicity of the monomethylating agent temozolomide by approximately threefold and tenfold, in HT29 and Colo205 colorectal tumour cell lines, respectively.



(iii)

The nuclear enzyme poly(ADP-ribose) polymerase (PARP) has an important role in the repair of DNA strand breaks, such as those caused by chemotherapeutic agents targeting DNA. Inhibition of PARP in tumour cells could, therefore, potentiate radiotherapy and DNA-targeted chemotherapy, making PARP an attractive target for cancer drug design. Golding and coworkers have reported the synthesis of a range of 1*H*-benzimidazole-4-carboxamides evaluated as PARP inhibitors[4]. Knowledge of the SARs for 2-aryl-1*H*-benzimidazole-4-carboxamides has been enhanced by X-ray crystallographic studies of the complex between 2-(3-methoxyphenyl)-1*H*-benzimidazole-4-carboxamide and the catalytic domain of chicken PARP. In addition, 2-(4-hydroxyphenyl)-1*H*-benzimidazole-4-carboxamide **(iv)** was found to potentiate the cytotoxicity of both temozolomide and topotecan against A2780 human ovarian carcinoma cells *in vitro*.



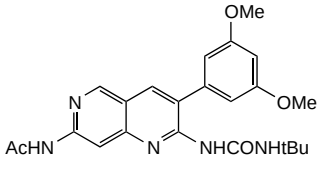
(iv)

3 Griffin, R.J. *et al.* (2000) Resistance-modifying agents. 8. Inhibition of *O*^{6}-alkylguanine-DNA alkyltransferase by *O*^{6}-alkenyl-, *O*^{6}-cycloalkenyl-, and *O*^{6}-(2-oxoalkyl)guanines and potentiation of temozolomide cytotoxicity *in vitro* by *O*^{6}-(1-cyclopentenylmethyl)guanine. *J. Med. Chem.* 43, 4071–4083

4 Golding, B.T. *et al.* (2000) Resistance-modifying agents. 9. Synthesis and biological properties of benzimidazole inhibitors of the DNA repair enzyme poly(ADP-ribose) polymerase. *J. Med. Chem.* 43, 4084–4097

Potent and selective inhibitors of the FGF receptor-1 tyrosine kinase

The inhibition of fibroblast growth factor (FGF) could be an effective strategy in prevention of the inappropriate vascularization that is characteristic of angiogenesis in solid tumours. The FGF-receptor-1 tyrosine-kinase is the most predominant FGF-receptor subtype in vascular cells, and its abnormal expression has been shown to correlate to prostate epithelial tumourigenicity *in vivo*. Although the crystal structure of the receptor (alone or complexed with ATP) is known, few selective inhibitors of FGF-receptor tyrosine-kinases have been reported. Denny and coworkers have described the synthesis and antitumour evaluation of a series of 3-aryl-1,6-naphthyridine-2,7-diamines and related 2-urea derivatives, as selective FGF-receptor-1 tyrosine-kinase inhibitors[5]. The studies were designed to assess the importance of the pyrimidine-ring aza atoms of the novel pyrido[2,3-*d*]pyrimidine, PD166866, a known ATP-competitive FGF-receptor-1 tyrosine-kinase inhibitor, and to develop compounds with improved potency, water solubility and bioavailability. In particular, the acetamide derivative **(v)** was a particularly potent inhibitor *in vitro* of human umbilical vein endothelial cell (HUVEC) microcapillary formation and Matrigel invasion, and showed significant *in vivo* delayed tumour growth in a highly vascularized mammary adenocarcinoma 16/c model at non-toxic doses.



(v)

5 Denny, W.A. *et al.* (2000) 3-(3,5-Dimethoxyphenyl)-1,6-naphthyridine-2,7-diamines and related 2-urea derivatives are potent and selective inhibitors of the FGF receptor-1 tyrosine kinase. *J. Med. Chem.* 43, 4200–4211

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