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.**

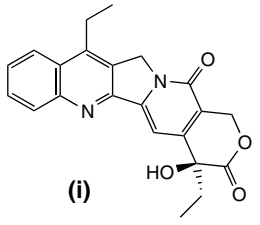
Chemistry

Antitumour molecules

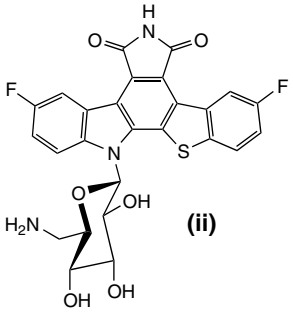
Fluoroindolocarbazoles as selective topoisomerase I active antitumour agents

Inhibitors of topoisomerase enzymes (topo I or topo II) have a well-established clinical role in anticancer chemotherapy. In the cell, topo I is involved in the formation of transient breaks in single-stranded DNA to relieve the torsional strain that develops during DNA replication or transcription. Known topo I inhibitors effectively stabilise these transient intermediate structures and thereby inhibit cellular proliferation. The observation that topo I levels are generally higher in cancer cells than in normal cells provides a rationale for their use in cancer chemotherapy; however, as with other classes of cytotoxic agents, the side effects associated with their use can be severe. The identification of the antitumour activity of camptothecin (CPT, **i**) [1] led to CPT and its analogues, such as irinotecan [2], occupying the dominant position in the topo 1 inhibitor market.

Balasubramanian and co-workers (Bristol–Myers Squibb Pharmaceutical Research Institute; http://www.bms.com) have reported the synthesis and *in vitro* and *in vivo* antitumour evaluation of a series of new glycosylated fluoroindolocarbazoles as selective topo I inhibitors [3]. Previous studies by the same group led to the discovery of the indolocarbazole class of compounds (represented by rebeccamycin) as non-camptothecin topo I selective agents [4]. Several of these new fluoroindolocarbazole analogues were found to have selective topo I inhibitory activity, aqueous solubility and *in vivo* activity against human xenograft antitumour animal models.



(i)



(ii)

In particular, the favourable pharmacokinetic profile of **ii**, which includes high levels of exposure in plasma and tumour, translated into broad spectrum *in vivo* activity against human colon (HCT116 and HCT29), ovarian (A2780) and, most notably, slow-growing human prostate (PC3) xenograft models. Notable features in the PC3 xenograft model included full responses (i.e. tumour completely disappeared) and superior efficacy over irinotecan. Based on the impressive topo I inhibitory activity, pharmacokinetic profile and *in vivo* xenograft activity exhibited by **ii**, this compound has been selected as a potential clinical candidate for cancer chemotherapy.

1 Wall, M.E. (1998) Camptothecin and taxol: discovery to clinic. *Med. Res. Rev.*18, 299–314
2 Bissery, M.C. *et al.* (1996) Experimental antitumor activity and pharmacokinetics of the camptothecin analog irinotecan (CPT-11) in mice. *Anticancer Drugs* 7, 437–460
3 Balasubramanian, B.N. *et al.* (2004) Design and synthesis of a fluoroindolocarbazole series as selective topoisomerase I active agents. Discovery of water-soluble 3,9-difluoro-12,13-dihydro-13-[6-amino-β-D-glucopyranosyl]-5*H*,13*H*-benzo[*b*]-thienyl[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione (BMS-251873) with curative antitumor activity against prostate carcinoma xenograft tumor model. *J. Med. Chem.* 47, 1609–1612
4 Long, B.H. *et al.* (2000) Non-camptothecin topoisomerase I active compounds as potential anticancer agents. *Expert Opin. Ther. Pat.* 10, 635–666

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