monitor

MOLECULES

Benzothiazole derivatives as antitumour agents

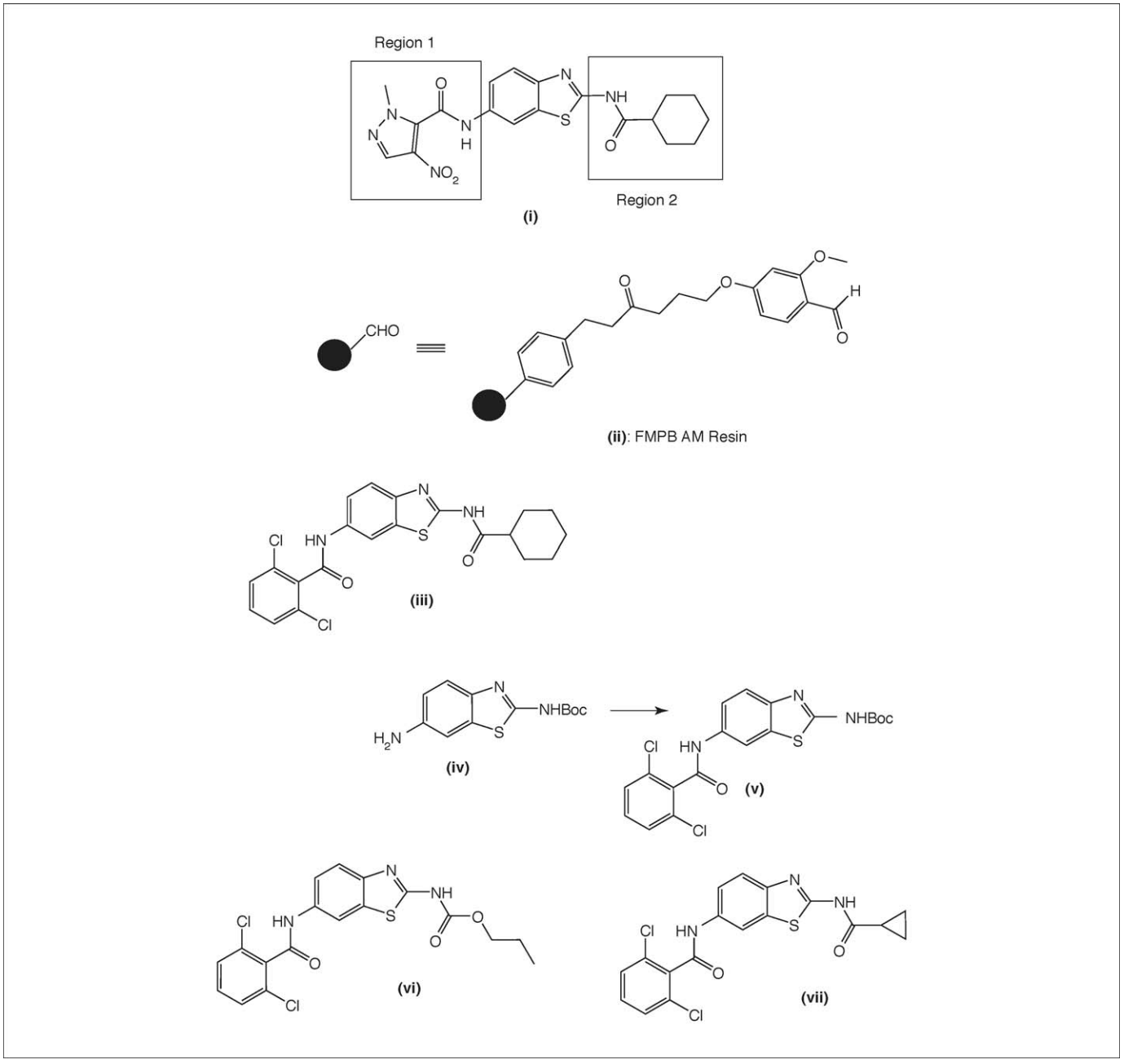
Cancer is projected to become the leading cause of mortality within the USA in the near future; it is currently the second-leading cause of death after cardiovascular disease [1]. Consequently, there is a great unmet medical need for new anticancer small-molecule therapeutics.

Workers at Sankyo, Japan, have performed a file-screen of their compound repository and have identified **(i)** as one of the most promising screening hits [2]. Although this compound displayed good potency and selective cytotoxicity against a tumourigenic cell line [WI-38 VA-13 subline 2RA (VA-13)], with an EC_{50} of 26 ng/ml, the results of an *in vivo* antitumour test was disappointing. The lack of activity *in vivo* was ascribed to poor metabolic stability of compound **(i)**. The focus of work here was, therefore, to improve metabolic stability, first by preparing a solid-phase library to vary the acylating group in region 1, then a parallel solution-phase library synthesis for optimization of region 2 by acylation of the exocyclic nitrogen. For the solid-phase chemistry, a polystyrene supported BAL-type linker [4-(4-formyl-3-methoxyphenoxy)butyrylamide] resin **(ii)** (FMPB AM resin, Novabiochem) was utilized to synthesize 200 compounds. Individual library members were identified by radio frequency encoding using IRORI^{TM} tags and MiniKan^{TM} technologies. Compounds synthesized were screened for selective cytotoxicity against a tumourigenic cell line (WI-38 VA-13 subline 2RA VA-13), and screening delivered a number of potent compounds.

One of the most potent compounds from this first library was **(iii)**, which displayed an EC_{50} of 15 ng/ml in the cytotoxicity assay. For the solution-phase library **(iv)** was acylated with the optimum acylating agent (2,6-dichlorophenyl-) identified from the first solid-phase library [contained within **(iii)**], to give **(v)**. After treatment with acid to reveal the primary (exocyclic) amine unit, this group was acylated with a variety of acylating agents.

After screening against the same selective cytotoxicity assay, one of the most potent compounds isolated was **(vi)**, which displayed an EC_{50} of 2.5 ng/ml. Returning to the original goal of improved metabolic stability, compound **(vii)** was chosen for pharmacokinetic studies in mice. This compound, although no more potent than the optimized acylated analogue from the first solid-phase library **(iii)** [EC_{50} of 15 ng/ml for **(iii)** compared to an EC_{50} of 13 ng/ml for **(vii)**], displayed significantly better metabolic stability: **(vii)** $t_{1/2}$ = 3.29 h, compared with the original screening hit **(i)** ($t_{1/2}$ = 0.53 h) and compound **(iii)** ($t_{1/2}$ = 1.1 h). Replacing the nitro (acyl) group of the initial screening hit **(i)** to give the dichloro derivative **(iii)** improved metabolic stability, and replacing the lipophilic cyclohexyl group of **(iii)** with the cyclopropyl group to give **(vii)** further improved metabolic stability. Compound **(vii)** demonstrated a strong inhibitory effect on tumour growth *in vivo*, with a single dosing at 20 mg/kg. Further work in this area, to continue to improve the *in vivo* properties of these novel antitumour agents, is warranted.

1359-6446/06/$ - see front matter doi:10.1016/j.drudis.2006.05.006



1 Gibbs, J.B. (2000) Mechanism-based target identification and drug discovery in cancer research. *Science* 287, 1969–1973

2 Yoshida, M. *et al.* (2005) Synthesis and biological evaluation of benzothiazole derivatives as potent antitumor agents. *Bioorg. Med. Chem. Lett.* 15, 3328–3332

Paul Edwards
mepauledwards@fsmail.net