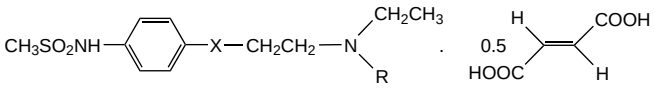

(iii) X = $CH(OH)CH_2$ R = $(CH_2)_6CH_3$

(iv) X = (*S*)-$CH(OH)CH_2$ R = $(CH_2)_5C(CH_3)_2F$

tachyarrhythmia (PVT), known as *torsade de pointes*.

When tested in clinical studies, ibutilide fumarate **(iii)**, a marketed class III representative, showed an incidence of *torsade de pointes* lower than 8%. However, the drug suffered by a rapid first-pass metabolism and could only be given by intravenous administration. On these bases, Hester and coworkers[4] have recently published a series of ibutilide analogues, modified at the heptyl side chain, which is the first responsible for metabolic degradation in the model compound. Modifications included the incorporation of alkyl, cycloalkyl, hydroxy, acetoxy and fluoro substituents. Their metabolic stability was initially evaluated *in vitro* by incubating the compounds with human liver microsomes. Preliminary results on rabbit heart preparations indicated the importance of the fluorine substitution. In particular, compound **(iv)** was devoid of proarrhythmic activity in a rabbit proarrhythmia model and was chosen for further evaluation in two canine models of re-entrant arrhythmias. The compound showed interesting activity and is currently undergoing clinical evaluation for the treatment of atrial arrhythmias.

2 Morgan, P.H. *et al.* (1976) Arrhythmias and antiarrhythmic drugs: mechanism of action and structure–activity relationship. *J. Pharm. Sci.* 65, 467–482

3 The Cardiac Arrythmia Suppression Trial (CAST) Investigators (1989) Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *New Engl. J. Med.* 321, 406–412

4 Hester, J.B. *et al.* (2001) Progress towards the development of a safe and effective agent for treating re-entrant cardiac arrhythmias: synthesis and evaluation of ibutilide analogues with enhanced metabolic stability and diminished proarrhythmic potential. *J. Med. Chem.* 44, 1099–1115

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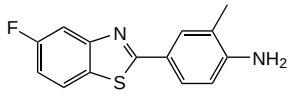
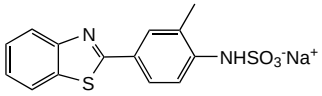
Novel antitumour molecules

Potent and selective antitumour benzothiazoles

The 3′-substituted 2-(4-aminophenyl) benzothiazole series possess, in a consistent pattern, potent antitumour activity (GI_{50} = < 1nM) in certain sensitive human cancer cell lines only (e.g. breast MCF-7, MDA-468; renal TK-10; ovarian IGROV-1). Other notable features of this class of agent include the unique biphasic dose–response relationship in sensitive cell lines, with cell kill occurring at low nanomolar concentrations, followed by a proliferative response (second growth phase) at low micromolar concentrations. It has been postulated that the second growth phase might be elicited by a metabolite that inactivates the bioactivating enzyme, cytochrome P450 CYP1A1; for the 3′-methyl substituted member of the series, the corresponding 6-hydroxylated metabolite has been identified to fulfil this role. To thwart deactivating metabolism, a series of fluorinated 2-(4-aminophenyl)benzothiazoles have been synthesized and evaluated as antitumour agents by Stevens and coworkers (Cancer Research Laboratories, University of Nottingham, UK)[1]. The fluorinated analogues retained the potency and selectivity *in vitro* of the parent non-fluorinated analogues, whereas in certain cases (5- and 7-fluorination) abolished the biphasic dose–response relationship. The most potent broad-spectrum agent in this series, 2-(4-amino-3-methylphenyl)-5-fluorobenzothiazole **(i)** is now the focus of pharmaceutical and preclinical development.



(i)



(ii)

A potential problem concerning the clinical use of these agents is posed by their lipophilicity, which presents limitations on drug formulation and bioavailability. This is because an aqueous intravenous formulation is desired to minimize the possibility of first pass deactivating metabolism. A further paper by Stevens and coworkers[2] describes the synthesis and physicochemical properties of sulfamate salt derivatives, (e.g. **ii**), of 2-(4-aminophenyl)benzothiazoles as potential (water-soluble) prodrugs for parenteral administration. These novel salts were found to be sparingly soluble under aqueous conditions (pH 4–9), and degradation to the free bioactive amine occurred under strongly acidic conditions.

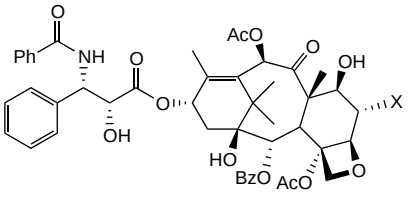
1 Stevens, M.F.G. *et al.* (2001) Antitumor benzothiazoles. 14. Synthesis and *in vitro* biological properties of fluorinated 2-(4-aminophenyl)benzothiazoles. *J. Med. Chem.* 44, 1446–1455

2 Stevens, M.F.G. *et al.* (2001) Antitumour benzothiazoles. 15. The synthesis and physicochemical properties of 2-(4-aminophenyl)benzothiazole sulfamate salt derivatives. *Bioorg. Med. Chem. Lett.* 11, 1093–1095

1359-6446/01/$ – see front matter PII: S1359-6446(01)01836-0

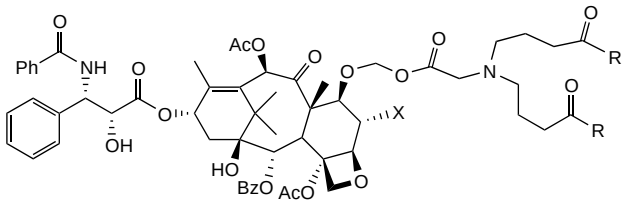
Paclitaxel developments

The metabolic fate of the clinical anticancer agent paclitaxel, has been elucidated in humans, rats and mice, and the major human metabolite, 6-α-hydroxypaclitaxel, found to be 30-times less active than paclitaxel itself. Blockade of this metabolic pathway has been postulated to provide taxanes with improved therapeutic efficacy and reduced clearance. Wittman and coworkers at the Bristol-Myers Squibb Pharmaceutical Research Institute (Wallingford, CT, USA)[3], have introduced α-halogen (X = F, Cl, Br) substituents **(iii)** into this position to block this deactivating hydroxylation, a strategy with some parallels to the fluorinated benzothiazoles report[1]. The new analogues were found to be approximately equipotent with paclitaxel itself (*in vitro* analysis in human colon cell line HCT116) but did not form detectable metabolites when analyzed in a human liver S9 fraction capable of hydroxylating paclitaxel.



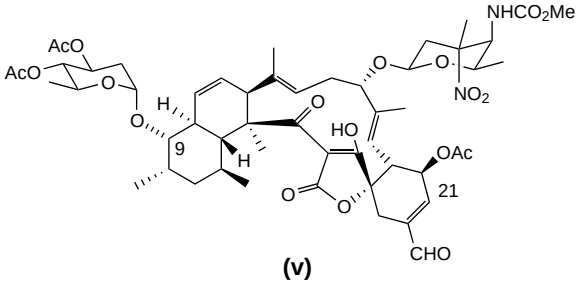
(iii)

The synergistic combination of paclitaxel with other antitumour agents, (e.g. alkylating agents), has been well-recognized to provide effective treatment regimes, and a further paper from the same group describes the syntheses and antitumour activity of three paclitaxel–chlorambucil hybrids[4]. In general, hybrid molecules are not as effective as combination therapy because optimization of individual drug concentrations and schedules is not possible; however, there might be potential advantages if both drugs can be deactivated as a result of the linking function, and then released together. Of the three hybrids prepared, compound **(iv)** showed significant *in vivo* activity in M109 and the paclitaxel resistant M109/taxIR model that was superior to single agent or combination treatment.



(iv)

R = $(CH_2)_3C_6H_4$-4-$N(CH_2CH_2Cl)_2$



(v)

3 Wittman, M.D. *et al.* (2001) Synthesis of metabolically blocked paclitaxel analogues. *Bioorg. Med. Chem. Lett.* 11, 809–810

4 Wittman, M.D. *et al.* (2001) Synthesis and antitumor activity of novel paclitaxel-chlorambucil hybrids. *Bioorg. Med. Chem. Lett.* 11, 811–814

Tetrocarcin derivatives as selective Bcl-2 inhibitors

Bcl-2 is a membrane protein that is frequently overexpressed in human cancers. It inhibits apoptosis induced by a variety of stimuli. In many cases, cancers overexpressing Bcl-2, such as follicular lymphoma and hormone-refractory prostate cancer, are also resistant to conventional chemotherapeutic agents. Recently, tetrocarcin, originally discovered as an antibiotic against Gram-positive bacteria, has been reported as the first small-molecule inhibitor of the anti-apoptotic function of Bcl-2. The absence of Bcl-2 family proteins in bacteria suggests that the antibacterial activities of tetrocarcin are not related to its activity against Bcl-2. Kaneko and coworkers at Kyowa Hakko Kogyo (Tokyo, Japan), have reported the synthesis and evaluation of novel tetrocarcin analogues to increase their selectivity against Bcl-2 (Ref. 5). It was found that 21-acetoxy-9-glycosyloxy derivatives, such as **v,** had potent Bcl-2 inhibitory activity without significant antimicrobial activity.

5 Kaneko, M. *et al.* (2001) Synthesis of tetrocarcin derivatives with specific inhibitory activity towards Bcl-2 functions. *Bioorg. Med. Chem. Lett.* 11, 887–890

Novel telomerase inhibitors

Telomeres are the guanine-rich, repeat sequences of TTAGGG that constitute the termini of human chromosomes. In most human somatic cells, telomeres shorten progressively with each cell division, leading ultimately to senescence and growth arrest. By contrast, most cancer cells acquire indefinite replicative capacity leading to cellular immortality through expression of telomerase, an enzyme that catalyzes addition of telomeres and maintenance of telomere length. Specific inhibition of telomerase, without affecting DNA polymerases and reverse transcriptases (such as *Taq* polymerase), represents an attractive therapeutic strategy against cancer cells. Despite intensive research efforts, no clinical trials of telomerase inhibitors have been initiated to date. Shin-ya and coworkers at the University of Tokyo (Tokyo, Japan), have reported the isolation of a potent, specific telomerase