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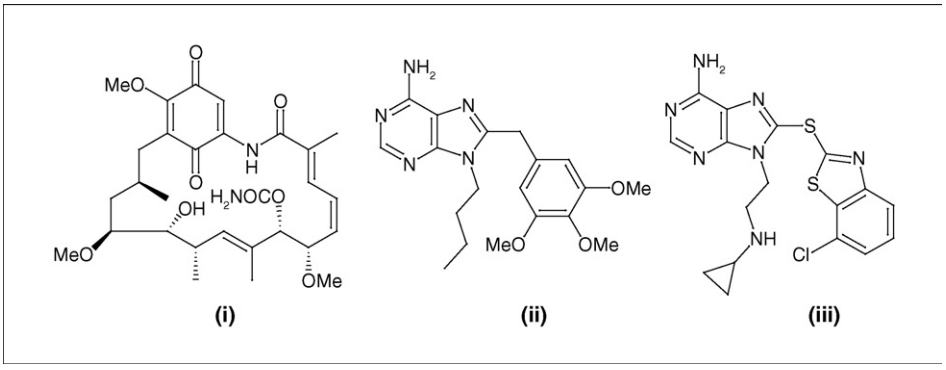
MOLECULES

Novel antitumour agents: antitumour activity of potent inhibitors of heat shock protein 90

Heat shock protein 90 (Hsp90) has emerged as an attractive molecular target for the potential treatment of a range of diseases such as cancer and inflammation where unregulated cell signalling, proliferation and survival are pivotal factors [1]. The key function of Hsp90 is to maintain client proteins in the correct folding conformation; and Hsp90 inhibition leads to rapid proteosomal degradation of such clients. Several Hsp90 client proteins are clinically validated cancer-drug targets (e.g. Her-2, AKT and Raf-1), further validating Hsp90 as an anticancer drug target.

Among small-molecule Hsp90 inhibitors, the semisynthetic ansamycin 17-allylamino geldanamycin **(i)** has been examined clinically [2]. More-recent studies have identified novel non-natural product-based inhibitors such as PU3 **(ii)** that possess affinity for the ATP-binding site of Hsp90 and show activity against tumour cells [3].

As part of efforts to further optimize the purine pharmacophore to increase solubility, potency and oral bioavailability, Zhang and co-workers (Conforma Therapeutics, San Diego, USA) [4] have reported the synthesis and antitumour evaluation of a series of Hsp90-inhibitory benzothiazolothio- and pyridinothiazolthio-purines. Activities of new compounds were determined by their ability to degrade the Hsp90 client protein Her-2. Some of the new compounds (containing a 7′-halogen substitutent) were found to exhibit low nanomolar activity in the Her-2 degradation assay (i.e. IC_{50}s 28–150 nM), correlating to cell-growth inhibition in breast cancer MCF7 cells. Consideration of key pharmaceutical characteristics such as solubility and oral bioavailability were considered for the most potent compounds. Based on superior pharmacokinetic parameters in mice, after oral administration at 100 mg/kg, compound **iii** was taken forward for *in vivo* evaluation in a tumour-xenograft growth-inhibition study. Following oral administration at 200 mg/kg, five days/week, 56% tumour-growth inhibition was observed compared to the control group. Increasing the *in vivo* potency for oral administration, and further development of this class of agent, are anticipated.



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Andrew D. Westwell
westwella@cf.ac.uk

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