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Synthesis and biological evaluation of novel analogues of batracylin with synthetic amino acids and adenosine: an unexpected effect on centromere segregation in tumor cells through a dual inhibition of topoisomerase IIα and Aurora B†

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In the search for new anticancer agents we designed and synthesized batracylin derivatives with linking synthetic amino acid side chains of different lengths and adenosine. Unexpectedly, we have found that in water and the culture media adenosine–amino acid–BAT conjugates form supramolecular structures and this prevents these compounds from entering cells. Consequently, these compounds exerted no biological activity when tested towards two human cell lines, lung adenocarcinoma (A549) and human leukemia (HL-60). In contrast, several amino acid–BAT precursors showed up to 25-fold enhanced cytotoxic activity compared to BAT and these compounds strongly interfered with DNA topoisomerase II activity and its cellular functions. In particular, these conjugates inhibited centromere segregation during mitosis in drug-treated tumor cells by preventing topoisomerase II-dependent Aurora B activation.

Introduction

Medicinal chemists continue to develop novel cytotoxic agents with new and unique mechanisms of action, however, many of these compounds still lack tumor selectivity or have not been therapeutically useful due to undesired toxic effects or low bioavailability *in vivo*. Apart from this classical approach to design and synthesize new molecules with antitumor activity, there is yet another line of activity in medicinal chemistry to combine different molecules with defined functions and activities to produce the so-called 'functionalized' molecules or drugs. In this approach, one can conjugate cytotoxic drugs with other molecules such as *e.g.* monoclonal antibodies which bind to specific cellular markers on the surface of tumor cells and offer an alternative therapy that is tumor-specific and/or less toxic. This direction has recently attracted a great deal of attention (for review see Chari 2008).[1] Another example can be to synthesize 'functionalized' cytotoxic molecules by combination of with other small molecules, such as proteins, peptides or sugars.

Batracylin (8-aminoisoindolo[1,2-*b*]quinazolin-12(10*H*)-one, BAT) exhibits excellent antitumor properties[2–5] and inhibits the catalytic activity of DNA topoisomerases that leads to production of DNA breaks and induction of the unscheduled DNA synthesis (UDS) in nonproliferating cells.[6,7] At the same time, in pre-clinical studies BAT produced severe toxicity in rats and mice. In addition, even between rodents different toxicity of BAT was observed and oral administration batracylin to rats was found to significantly more toxic, compared to mice. The BAT toxicity observed across all studied species was caused by presence of its toxic metabolite, *N*-acetyl-batracylin (ABAT), following metabolism mediated by *N*-acetyl-transferase 2 (NAT2).[8–10] First-in-human study was conducted in pharmacogenetically selected thirty-one patients with advanced refractory solid tumors and lymphomas and a slow acetylator NAT2 genotype.[11] The objectives included determination of the safety, tolerability, maximum tolerated dose (MTD) and pharmacokinetics (PK) of batracylin and its metabolites. Although no objective responses were observed, even at doses of BAT as high as 400 mg per day for 7 days (in a 28 day cycles), patients tolerated doses which were about 20-fold higher than the MTD in rats and 70% of the MTD in mice.

The low water solubility of BAT, its high toxicity as well as large doses required for anticancer activity, are the causes that

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