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Biological activity of conjugates of muramyl dipeptides with batracylin derivatives

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Abstract

Antitumour activity of batracylin (BAT), muramyldipeptide (MDP) and four immunomodulatory conjugates of BAT with MDP were evaluated in the study. The activity was assessed using viability tests performed in the cultures of tumour cell lines of different tissue origin such as WEHI 164 (fibrosarcoma), K562 (leukaemia), and Ab (melanoma), populations of immune cells isolated from peripheral blood, and the tumour cells mixed with immune cells. An intensity of cell death caused by the analogues was measured using flow cytometry analysis as subG1 peak and the distinction between necrotic and apoptotic DNA cleavage during cell death was performed using DNA fragmentation assay. The compounds **11c**, **11e** and **11h** managed to kill WEHI 164 cells in the presence of immune cells in apoptotic manner while BAT and conjugate **11a** caused necrosis at the same time. Necrotic pattern of DNA cleavage was also noted in all cultures containing K562 and Ab cells. BAT and MDP caused necrosis in the cultures of pure immune cells, while the conjugates did not affect these cultures at all. Surprisingly, some analogues increased viability of K562 and Ab cells.

Low toxicity and ability to induce apoptosis suggested usefulness of some analogues, mainly **11c**, as antitumour drugs in limited range of tumours of certain tissue origin, such as WEHI 164.

Keywords: Muramylodipeptides; Batracylin; Immunomodulation

1. Introduction

Batracylin (8-aminoisoindolo-[1,2-*b*]quinazolin-1,2-(10*H*)-one, BAT) is a heterocyclic water insoluble agent which is believed to inhibit enzymatic activity of topoisomerase II in ATP-insensitive manner. It causes cleavage of DNA and stimulates unscheduled DNA synthesis [1]. These properties are likely to be

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