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Research paper

# Synthesis of functionalized new conjugates of batracylin with tuftsin/retro-tuftsin derivatives and their biological evaluation

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ABSTRACT

New batracylin conjugates with tuftsin/retro-tuftsin derivatives were designed and synthesized using T3P as a coupling agent. The conjugates possess an amide bond formed between the carboxyl group of heterocyclic molecule and the *N*-termini of the tuftsin/retro-tuftsin chain. The *in vitro* cytotoxic activity of the new analogues and their precursors was evaluated using a series of human and murine tumor cells. BAT conjugates containing retro-tuftsin with branched side aminoacid chain, in particular with leucine or isoleucine, were about 10-fold more cytotoxic toward two human tumor cell lines (lung adenocarcinoma (A549) and myeloblastic leukemia (HL-60)). These compounds showed about 10-fold increased cytotoxicity against the two types of tumor cells compared to parent BAT. We have not observed important differences in the mechanism of action between BAT and its cytotoxic tuftsin/retro-tuftsin conjugates. We propose that high biological activity of the most active BAT conjugates is a result of their greatly increased intracellular accumulation.



## 1. Introduction

Batracylin (8-aminoisoindolo[1,2-b]quinasolin-12(10*H*)-one, BAT) [1] is a heterocyclic amine identified by the drug screening system at the National Institutes of Health (Bethesda, USA) [2]. In preclinical studies, BAT showed high antitumor and cytotoxic activity toward several experimental tumor cell models, including cells which are resistant to standard chemotherapeutics, such as doxorubicin, methotrexate and cisplatin [3–8]. In the recently completed phase I clinical studies, safety profiles of BAT were evaluated in human cancer patients. These studies showed that BAT is well tolerated by human patients up to 400 mg/kg and provided some encouraging data concerning its therapeutic potential [9].

One of the new directions in the synthesis of novel chemical entities with antitumor activity is to combine several different molecules with different functions and/or activities to produce functionalized derivatives [10,11]. The aim of this approach is to obtain compounds with enhanced activity/specificity and improved pharmacologies properties, including increased bioavailability and lowered general toxicity of the conjugate. We recently set out a program aimed at the synthesis of new BAT-tuftsin/retro-tuftsin conjugates which were expected to have improved pharmacological features (such as increased water solubility, lowered general toxicity *in vivo*) and potentially have additional mechanisms of action, including immunostimulatory effect of tuftsin. Tuftsin is a tetrapeptide Thr-Lys-Pro-Arg (TKPR) that been shown to possess immunologic, tumoricidal, and bactericidal activities [12–14]. Accordingly, tuftsin has been successfully used in combination with different antibiotics to treat opportunistic infections caused by bacteria, fungi, and viruses. In addition, it also showed antineoplastics properties [15–32]. Moreover, tuftsin binds to the receptor neuropillin-1 (NRP1) on the surface of cells that participates in several different signalling pathways controlling cell migration and survival [33].

We report here the synthesis of a new series of BAT analogues with tuftsin/retro-tuftsin derivatives containing isopeptide bond between ε-amino group of lysine and carboxyl group of aliphatic amino acids such as Gly, Ala, Val, Leu, Ile. In our method, synthesis of new analogues is based on the modification in the *C*-terminus of the peptide residue by the formation of an amide bond between the

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