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RESEARCH ARTICLE

Synthesis and Biological Evaluation of Acridine/Acridone Analogs as Potential Anticancer Agents

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Abstract: ***Background*:** The lack of efficacious therapy for advanced melanoma and neuroblastoma makes new approaches necessary. Therefore, many scientists seek new, more effective, more selective and less toxic anticancer drugs.

***Objective*:** We propose the synthesis of the new functionalized analogs of 1-nitroacridine/4-nitroacridone connected to tuftsin/retro-tuftsin derivatives as potential anticancer agents.

***Methods*:** Acridine and acridone analogues were prepared by Ullmann condensation and then cyclization reaction. As a result of nucleophilic substitution reaction 1-nitro-9-phenoxyacridine or 1-chloro-4-nitro-9(10*H*)-acridone with the corresponding peptides, the planned acridine derivatives (**10a-c**, **12**, **17-a-d**, **19**) have been obtained. The cytotoxic activity of the newly obtained analogs were evaluated against melanotic (Ma) and amelanotic (Ab) melanoma cell lines and neuroblastoma SH-SY5Y by using the XTT method. Apoptosis and cell cycle were analyzed by flow cytometry.

***Results*:** Among the investigated analogs compound 12 exhibited the highest potency comparable to dacarbazine action for amelanotic Ab melanoma cells. FLICA test (flurochrome-labeled inhibitors of caspases) showed that this analog significantly increased the content of cells with activated caspases (C+) among both neuroblastoma lines and only Ab melanoma line. Using phosphatidylserine (PS) externalization assay, 12 induced changes in the Ab melanoma plasma membrane structure as the externalization of phosphatidylserine (An+ cells). These changes in neuroblastoma cells were less pronounced.

***Conclusion*:** Analog 12 could be proposed as the new potential chemotherapeutic against amelanotic melanoma form especially.

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1. INTRODUCTION

Cancer, which is mostly caused by a mutation of a normal cell, is one of the most common malignant diseases obsessing mankind [1, 2]. Tumor cells resistance to many anticancer drugs is a huge concern for effective cancer chemotherapy [3]. Hence, there is a high demand to develop new drugs with improved pharmacological properties, enhanced antitumor activity and lower toxicity. Acridines have attracted considerable interest because of their broad range of biological activity. Initially, acridine derivatives were applied as pigments and dyes [4]. The first clinical application of acridines was targeted against bacterial [5] and parasitic [6] infections. Their anticancer properties were discovered in the 70s [7, 8]. Actually, the anticancer activity of acridine/acridone analogs has attracted incoming interest. To date, many derivatives of acridine were synthesized and tested for antitumor activity [9, 10].

One of the ways to effective delivery of drugs to the target site in the body is using carrier-drug conjugates, in which the active ingredient is bound by a covalent bond with a carrier, *e.g.* peptides [11]. One of such peptides is tuftsin (TKPR), natural tetrapeptide, present in the peripheral blood of humans and other mammals, where it stimulates certain white blood cells [12]. The activity of tuftsin is generally directed to the activation of non-specific elements of the immune system.

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