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Solid Phase Synthesis and Biological Activity of Tuftsin Conjugates

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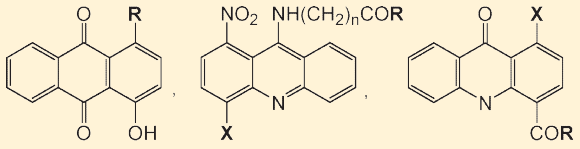
Supporting Information

ABSTRACT: New tuftsin/retro-tuftsin conjugates were designed and synthesized using a classical fluorenylmethoxycarbonyl (Fmoc) solid phase procedure. All the peptide conjugates were divided into three series: 1,4-dihydroxyanthraquinone (type A), 1-nitroacridine (type B), and 4-carboxyacridone (type C) derivatives. In type A conjugates, the N-terminal group of the peptide chain is directly connected to the anthraquinone ring at C1 (Scheme 1), whereas types B and C conjugates possess an amide bond formed between the carboxyl group of heterocyclic molecule and the N-termini of the tuftsin chain. The in vitro cytotoxic activity of the tuftsin conjugates and their precursors using two human tumor cell lines (lung adenocarcinoma (A549) and myeloblastic leukemia (HL-60)) was investigated. The analogues from groups A and C exhibited low cytotoxic activity, whereas several compounds of type B showed a potent and selective cytotoxic activity against tested tumor cell lines. None of the examined tuftsin conjugates demonstrated any significant effect on the catalytic activity of types I and II DNA topoisomerases.



R = Thr-Lys(**Y**)-Pro-Arg-OH
Arg-Pro-Lys(**Y**)-Thr-OH, **Y** = H, Gly, Ala, βAla, Val, Ile

n = 2, 3, 5, **X** = H, CH_3, NO_2

INTRODUCTION

Many acridine derivatives possess antimicrobial, antiviral, and anticancer properties.[1,2] These compounds are also known as biological fluorescent probes. Acridine derivatives are DNA-binding agents but also interact with other biological targets such as types I and II DNA topoisomerases, telomerase, polymerase, and protein kinases.[1,3] One of the acridine derivatives that showed potent anticancer properties was ledakrin (nitracrine). This compound was introduced into the clinic as an antitumor drug with unique activity against many solid tumors.[4] Unfortunately, ledakrin produced intense nausea and vomiting in cancer patients and was eventually withdrawn from clinical practice. Recently, new 4-methyl analogues of ledakrin and their analogues were synthesized and showed promising antitumor activity and much lower general toxicity.[5]

The second group of compounds, which has found clinical applications in the treatment of leukemia or solid tumors, is anthracycline antibiotics. However, these drugs, like many other chemotherapeutics, also show toxic effects such as high cardiotoxicity that limit their application as antitumor drugs. Search for novel anthracycline analogues with improved pharmaceutical properties led to the development of mitoxantrone, a second generation synthetic drug used in cancer therapy. However, similar to anthracyclines, mitoxantrone demonstrates cardiotoxic properties as a consequence of the generation of reactive oxygen species in living cells.[6−8]

It is well-known that an ideal chemotherapeutic agent should selectively target neoplastic cells with minimal adverse effects on healthy cells. One of the approaches that can lead to increased drug specificity is the design of peptide-based conjugates, where the peptidic component serves to selectively target tumor cells. Many peptide−drug derivatives showed increased specificity toward tumor cells and low general toxicity,[9−12] in part through their binding to specific receptors that are present on the cell surface.[9,13] These include peptides combined with anthraquinone and acridine/acridone derivatives that showed encouraging pharmacological properties.[1,3]

In this study, we applied tuftsin analogues as a peptidyl carrier of cytotoxic molecules. Tuftsin is a tetrapeptide (TKPR) that is liberated from the Fc domain of the heavy chain of immunoglobulin G (IgG) by two enzymes, leukokininase and spleen tuftsin endocarboxypeptidase. This peptide activates several components of the immune system, including granulocytes and macrophages.[14] Tuftsin has been successfully investigated as a coadministration agent with different antibiotics in the treatment of opportunistic infections caused by bacteria, fungi, and viruses, but it also showed antineoplastic properties.[15−17] Since tuftsin is prone to a rapid enzymatic degradation in the blood plasma,[18,19] we designed peptide conjugates containing tuftsin analogues modified at the ε-amino group of lysine to increase their blood plasma stability. We hypothesized that covalent combination of tuftsin analogues and anthraquinone or acridine/acridone derivatives will allow us to obtain conjugates with anticancer activity and improved selectivity toward tumor cells. In this paper, we present the solid-phase synthesis of new tuftsin conjugates with anthraquinone and acridine/acridone derivatives and evaluation of their cytotoxic activity as well as biological effects induced by these compounds in tumor cells.

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