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Synthesis of analogues of anthraquinones linked to tuftsin or retro-tuftsin residues as potential topoisomerase inhibitors

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Abstract: A novel group of [(4-, 5- or 8)-hydroxy-9,10-anthraquinone-1-yl]-(tuftsin or retro-tuftsin) acids and methyl esters has been synthesized as potential anticancer compounds. The corresponding protected tuftsin or retro-tuftsin derivatives were also synthesized. We hope that combining compounds of different mechanisms of action will improve their clinical properties, and that our new analogues will be much more effective against multidrug-resistant tumour cell lines. Copyright © 2006 European Peptide Society and John Wiley & Sons, Ltd.

Keywords: anthraquinone peptide derivatives; tuftsin; retro-tuftsin; synthesis

INTRODUCTION

Hundreds of anthraquinone derivatives have been synthesized to date [1]. Some of them exhibit very interesting and promising anticancer properties, e.g. mitoxantrone or ametantrone [2]. These compounds enable the interaction with DNA-metabolizing enzymes and the perturbation of the replication and transcription of genetic information process using enzymes topoisomerase I and II (topo I and II) as inhibitors [3–5]. Topoisomerase inhibition represents a key therapeutic target in chemotherapy. Doxorubicin and mitoxantrone have been shown to form cleavable complexes with topo II and camptothecin and its analogues with topo I [5,6]. Till now, several anthraquinone compounds exhibiting very interesting and promising anticancer properties have been synthesized, e.g. derivatives with unsymmetrical side chains [7], aza analogues containing pyridine [8] or pyridazine [9] rings and analogues possessing a five- or six-membered heterocyclic ring. Among them anthrapyrazoles [10] and their aza analoges [11], anthrapyridones, anthrapyridazones and benzo[*e*]perimidines have been designed and obtained [12]. Also, anthraquinone derivatives have been synthesized, which contained amino acid or peptide chains as topoisomerase inhibitors [5,13–16]. The clinical usefulness of anthracyclines is limited because of some drawbacks, such as cardiac toxicity and tumour resistance [1]. These drawbacks have stimulated scientists and clinicians to seek anticancer agents devoid of the mentioned shortcomings.

On the other hand, the tetrapeptide tuftsin (H-Thr-Lys-Pro-Arg-OH) [17] possesses significant immunomodulatory properties. It is capable of stimulating granulocyte and macrophage functions such as phagocytosis, motility, somnogenic response, as well as bactericidal and tumoricidal activity. Moreover, tuftsin has a number of other interesting biological properties, such as anti-infective, anticancer, anti-AIDS and growth factor activities [18,19]. It is possible that combining compounds showing different mechanisms of action may improve clinical properties of both components, so we hope that new analogues of anthraquinones and tuftsin will be much more effective against multidrug resistance (MDR) of tumour cell lines. MDR is one of the main obstacles in chemotherapy of cancer. The idea of combining these two biologically active compounds was based on the synergistic activity of muramyl dipeptide (MDP) [20,21]. This paper reports novel anthraquinone peptide analogues and the method of their syntheses. The results on the biological tests of these compounds will be reported in due course.

RESULTS AND DISCUSSION

Continuing our search for potential anticancer agents [20,22–25], we synthesized new anthraquinone analogues containing covalently bonded tuftsin or retro-tuftsin derivatives as potential topoisomerase inhibitors. We hope that combining these compounds (tuftsin – a well-known immunostimulator – and anthraquinone derivatives) with different mechanisms of action will improve their clinical properties and that these new analogues will be much more effective against MDR of cancer cells. The synthesis of the compounds was carried out according to Scheme 1. During the first step of the synthesis, 1,4-, 1,5- or 1,8-bis(tosyloxy)anthraquinone from 1,4-, 1,5- or 1,8-dihydroxy-anthraquinone and *para*-toluenesulfonyl chloride was obtained [26]. These

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