Synthesis and Antitumor Activity of Conjugates of Muramyldipeptide or Normuramyldipeptide with Hydroxyacridine/Acridone Derivatives

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Received July 10, 2002

A series of MDP (muramyldipeptide) or nor-MDP (normuramyldipeptide) analogues modified at the C-terminus post of the molecule by a formation of an ester bond between the carboxylic group of isoglutamine and the hydroxyl function of the respective derivatives of 4-carboxamide-acridine/9-acridone or 1-nitro-9-hydroxyalkylaminoacridines were synthesized as potential anticancer agents. The compounds *O*-(1-*O*-benzyl-*N*-acetyl-muramyl-L-alanyl-D-γ-isoglutaminyl)-9-(ethylamino)-1-nitroacridine ester **3j** and *O*-(1-*O*-benzyl-*N*-acetyl-muramyl-L-alanyl-D-γ-isoglutaminyl)-9-propylamino-1-nitroacridine ester **3k** exhibited high in vitro cytotoxic activity against a panel of human cell lines, prostate cancer and AIDS-related lymphoma (ARL). Analogue **3j** was also active in vivo in the hollow fiber assay. Antitumor activity of both compounds were tested in vivo against difference human tumor xenograft, but only analogue **3k** showed in vivo activity against sc UACC-62 melanoma in mice.

Introduction

Synthesis and antitumor activity of conjugates of MDP (muramyldipeptide) or nor-MDP (normuramyldipeptide) obtained in the acylation of the C6 hydroxyl group in the sugar moiety MDP by *N*-substituted acridine/acridone ω-aminoalkano-carboxylic acids and in the amide bond formation between the carboxylic group of isoglutamine and the amine function of the respective acridine/acridone derivatives have been already presented.[1] MDP and nor-MDP analogues modified with acridine/acridone derivatives in the peptide part demonstrated high cytotoxic activity, and two among them appeared to be active in vivo in the hollow fiber assay.[1]

The carboxyl group of MDP is a convenient site for chemical modifications that lead to derivatives that are interesting from the biological point of view. Among them are Murabutide (administered in clinical trials as adjuvants for vaccines), MDP-Lys(L18) (Muroctasin), and MTP-PE.[2] Due to Muroctasin activation of peripheral blood leukocytes, this particular compound is expected to be a useful drug for the treatment of leukopenia induced either by cancer chemotherapy or radiation therapy.[3] Muramyl tripeptide phosphatidylethanolamine (MTP-PE) stimulates in vitro and in vivo monocytes/macrophages to kill a variety of tumor cells. Encapsulation of MTP-PE into multilamellar liposomes (L-MTP-PE) is presently undergoing clinical trials in patients with recurrent osteosarcoma and melanoma. There is an expectation that L-MTP-PE combined with other anticancer agents may improve long-term cure rates of patients with these diseases.[4]

Continuing our program of syntheses of conjugates of MDP or nor-MDP with anticancer active compounds[1,5−8] we present syntheses of several new MDP or nor-MDP analogues which are modified at the C-terminus of the peptide residue by the formation of ester bond between the isoglutamine carboxylic group and the hydroxyl group of 4-carboxamide-hydroxyalkylacridine/9-acridone and 1-nitro-9-hydroxyalkylaminoacridines. 4-Carboxamide-acridine/9-acridone derivatives are known as effective anticancer agents. Among them *N*-[2-(dimethylamino)ethyl]acridine-4-carboxamide (DACA), a lipophilic DNA intercalating reagent synthesized in the laboratory of Auckland in New Zealand,[9] is a dual topoisomerase I/II poison[10] showing high in vivo activity against two experimental murine solid tumors, Lewis lung and Colon 38.[9,11] DACA is able to overcome transport multidrug resistance (MDR) mediated by both P-glycoprotein and multidrug resistance protein (MRP).[12−14] On the basis of both these properties, DACA has undergone clinical trials.[15,16] Unfortunately, clinically accepted 4-carboxamide-acridine/9-acridone derivatives with the strongest antitumor activity, such as DACA, could not be coupled to MDP, as they are devoided of functional groups capable of forming a covalent bond with the MDP molecule. Acridine/acridone moieties in the conjugates presented herein correspond to variously modified structures of acridine derivatives whose biological activities have not been evaluated. On the other hand, the 1-nitro-9-hydroxyalkylaminoacridines have high antineoplastic activity, which was confirmed by many tests in vitro and in vivo.[17] Pharmacological examination showed that they are less toxic than the other known derivatives of acridines. These compounds have been patented by B. Wysocka-Skrzela at al.[17] who adapted their use for the synthesis of some conjugates with MDP and nor-MDP. One of the derivatives of 1-nitro-9-hydroxyethylaminoacridine containing a methyl group at C4 was selected for preclinical studies for prostate cancer.[18]

Chemistry

The synthesis of 4-carboxamide-hydroxyalkylacridine/9-acridone and 1-nitro-9-hydroxyalkylaminoacridine con-

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10.1021/jm020991m CCC: $25.00
Published on Web 11/28/2002