SYNTHESIS AND CYTOTOXIC PROPERTIES OF NOVEL ALKYLATING DERIVATIVES OF L-PROLINE

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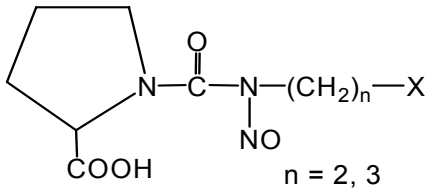
New alkylating derivatives of L-proline were synthesized as a prodrugs susceptible to the action of ubiquitously distributed, cytosolic imidodipeptidase – prolidase [E.C.3.4.13.9]. Although prolidase [E. C. 3. 4. 13. 9] is found in normal cells, substantially increased levels are found in some neoplastic tissues [1-4]. Because prolidase evokes ability to hydrolyse imido-bond of various low molecular weight compounds coupled to L-proline, we hypothesized that coupling of L-proline through imido-bond to an alkylating moiety might create prodrugs which would be locally activated by tumor-associated prolidase and consequently would be less toxic to normal cells that evoke lower prolidase activity [1-4].



n = 2, 3

X = Cl, Br

These compounds were used as substrates for prolidase activity assay. They were found as good substrates for prolidase, however with weak susceptibility. Their susceptibility were comparable to the well-known endogenous prolidase substrate, glycyl-L-hydroxyproline. We have compared several aspects of pharmacological actions of the alkylating derivatives of L-proline in MCF-7 and MDA-MB 231 breast cancer cells. Evaluation of the cytotoxicity of these compounds employing a MTT assay and inhibition of [^{3}H]thymidine incorporation into DNA in both MDA-MB-231 and MCF-7 breast cancer cells demonstrated that these compounds were more active than carmustine and chlorambucil. New alkylating derivatives of L-proline were compared for their effects on collagen and DNA synthesis in breast cancer MCF cells. Increased ability of these compounds to suppress the protein synthesis, compared to chlorambucil and carmustine, was found to be related to an inhibition of prolidase activity and expression.

[1] Chrzanowski K., Bielawska A., Pałka J.: Il Farmaco 58, 1113-1119 (2003)
[2] Bielawska A., Kosk K., Bielawski K.: Pol. J. Pharmacol. 53, 283-287 (2001)
[3] Bielawska A., Chrzanowski K., Bielawski K., Pałka J.: Pharmazie 56, 4, 290-294 (2001)
[4] Chrzanowski K., Bielawska A., Bielawski K., Wołczyński S., Pałka J.: Il Farmaco 56, 701-706 (2001)