

Design and Synthesis of Novel cyclopeptide Derivatives as New Cytotoxic Agents

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Abstract

A new series of anti-cancer agents based on cyclopeptide scaffold containing methyl sulfonyl group at the para position of the C-4 phenyl ring were synthesized and their cytotoxic activities were determined against several human cancer cell lines. compounds, c Glu-Ser-Pro-Lys-PhSO₂Me (1v), c Gly-Pro-Ala-Lys-PhSO₂Me (2v) c Ser-Glu-Gly-Pro-Lys-PhSO₂Me (3v) c Lys-Gly-Pro-Asp-PhSO₂Me (4v) c Asp-Gly-Pro-Lys-PhSO₂Me (5v) were synthesized and characterized by lc-mass spectroscopy and NMR. based on the results the most potent cytotoxic cyclicpeptide against A549 cell line was (1v) with IC₅₀ values 3.18 μM and the most potent cytotoxic cyclicpeptide against MCF-7 cell line was (5v) with IC₅₀ values 2.46 μM respectively, while most of the compounds had sufficient activity against MCF-7, HEPG-2, HT-29 and A-549 cell lines are with mean IC₅₀ values ranging from 2.46 to 31.44 μM.

Introduction: The logical design of this study was based on the use of pharmacophoric moiety of COX-2 inhibitors with aromatic or cyclic amino acids and acidic amino acids to simulate the structure of COX-2 inhibitors. As a result, it would be appealing to COX-2 inhibitors with peptide structure which show antitumor and anti-inflammatory effects.

Methods and Results: The results clearly indicated that modified cyclopeptides (1v - 5v), showed significant cytotoxic activity against all chosen cell lines. Compound (5v) showed a great anti-cancer activity against MCF-7 cell line and Compound (3v) showed a great anti-cancer activity against A549 cell line.

Conclusions:

In this study we synthesized 5 modified cyclopeptides by solid phase peptide synthesis approach and examined the cytotoxicity of them on 4 different cell lines. This study indicates that all synthesized compounds showed significant cytotoxicity against different cell lines specially against MCF-7 and A549 cell lines. In addition, modifications on the sequence of modified cyclopeptides had a significant influence on the cell cytotoxicity.

Key words: cyclopeptide/ Methyl sulfonyl / cytotoxic activity / MTT / Docking study

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