OpenAccess
www.openaccessjournals.com

Journal of Pharmaceutical Toxicology

Biological activity and apoptotic signaling pathway of C11-functionalized cephalostatin 1 analogues

Lubna Tahtamouni

Colorado State University, USA

Statement of the Problem: Cephalostatin 1, a potent anti-cancer agent, is a natural bis-steroidal alkaloid that causes cell death in the subnanomolar to picomolar ranges via an atypical apoptosis pathway. Although cephalostatin 1 is a highly effective anticancer drug, its availability limits its utilization. Previously, our group reported the synthesis of two 12'α-hydroxy derivatives of cephalostatin 1 and their ability to induce cell death by activating the atypical ER stress apoptosis signaling pathway. As part of our continuous investigation into developing active synthetic analogues of cephalostatin 1, we modified position C-11 by functionalization with an -OX group (X = Me, Et, H) of the bis-steroidal dimer 2.

Methodology: Six C11-functionalized cephalostatin 1 analogues (CAs) were synthesized and for the cytotoxic compounds, the induced apoptotic pathway was investigated by MTT assay, flow cytometry, clonogenic assay, qRT-PCR, Cytochrome C release assay and Western blotting.

Findings: The C11-functionalized cephalostatin 1 analogues 5 and 6 (CA5 and CA6) were found to exhibit cytotoxic activity against K-562 leukemia cells, MCF-7 breast cancer cells and DU-145 prostate cancer cells, while the remaining four analogues did not show anti-tumor activities against any of the cell lines. Our results indicated that CA5 and CA6 induced cell death via the atypical ER-dependent apoptosis pathway; they increased the expression of Smac/DIABLO, an inhibitor of inhibitors of apoptosis (IAPs), which in turn facilitated the activation of different caspases including the ER-caspase 4 without cytochrome c release from mitochondria.

Conclusion & Significance: CA5 and CA6 are promising anticancer agents due to their low GI50, the remarkable apoptosis pathway they induce which can overcome chemoresistance, and their very low toxicity to normal cells making them cephalostatin 1 utilizable alternatives.

Biography

Lubna Tahtamouni, a visiting senior research scholar at The Department of Biochemistry and Molecular Biology/ Colorado State University/USA, is a full professor at the Department of Biology & Biotechnology, the Hashemite University, Jordan, where she has been a faculty member since 2005. Her research studies cellular alternations leading to cancer for a better understanding of its initiation and development. This information can help in creating and improving cancer treatments. Her different projects focus on cell migration, adhesion and metastasis; mitochondrial function and apoptosis; cytoskeleton and related proteins; cell cycle and anti-tumor drug screening. She collaborates with other researches interested in basic, translational and clinical sciences..

Publications

Baguley B, Kerr D, Lu Y, Mahato R (2001) Anticancer drug development. Pharmaceutical Perspectives of Cancer Therapeutics 8:49-92.

Dirsch V, Müller I, Eichhorst S, Pettit G, Kamano Y, Inoue M, Xu J, Ichihara, Wanner, Vollmar A (2003) Cephalostatin 1 selectively triggers the release of Smac/DIABLO and subsequent apoptosis that is characterized by an increased density of the mitochondrial matrix. Cancer Research 63: 8869-8876.

Parrish A, Freel C, Kornbluth S (2013) Cellular mechanisms controlling caspase activation and function. Cold Spring Harbor Perspectives in Biology 5:1-25.

Pettit G, Inoue M, Kamano Y, Herald D, Arm C, Dufresne C, Christie N, Schmidt J, Doubek D, Krupa T (1988) Isolation and structure of the powerful cell growth inhibitor cephalostatin 1. Journal of the American Chemical Society 110:2006-2007.

Tahtamouni LH, Nawasreh MM, Al-Mazaydeh ZA, Al-Khateeb RA, Abdellatif RN, Bawadi RM, Bamburg JR, Yasin SR (2018) Cephalostatin 1 analogues activate apoptosis via the endoplasmic reticulum stress signaling pathway. European Journal of Pharmacology 818:400-409.

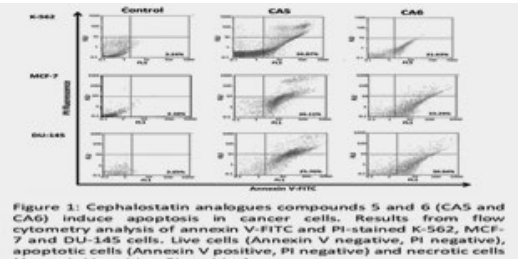

Figure 1: Cephalostatin analogues compounds 5 and 6 (CA5 and CA6) induce apoptosis in cancer cells. Results from flow cytometry analysis of annexin V-FITC and PI-stained K-562, MCF-7 and DU-145 cells. Live cells (Annexin V negative, PI negative), apoptotic cells (Annexin V positive, PI negative) and necrotic cells

Citation: Lubna Tahtamouni, *Biological activity and apoptotic signaling pathway of C11-functionalized cephalostatin 1 analogues*, Natural Products 2020, International Conference on Natural Products and Traditional Medicine, Amsterdam, The Netherlands, Webinar, 13th July,2020, pp: 16.