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TITLE

Pyrrolo[1,2-*b*][1,2,5] benzothiadiazepine 5,5-dioxides (PBTDS), an Experimental Anti- leukemic Compounds: Deciphering their Mechanism of Action

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The antitumor activity of pyrrolo[2,1-*c*][1,4]benzodiazepines (PBDs) related to anthramycin was extensively studied. It was hypothesized that anthramycin, like other DNA-alkylating agents, would induce apoptosis through a mitochondrial pathway. Pyrrolo[1,2-*b*][1,2,5]benzothiadiazepine 5,5-dioxides (PBTDS) induced apoptosis in human BCR-ABL expressing leukemia cells through the activation of the caspase-8,-9 and -3, and cleavage of poly(ADP-ribose) polymerase. The bax:bcl-2 ratio was increased as a consequence of down-regulation of bcl-2 and up-regulation of bax proteins in response to treatment with PBTDS. In addition, PBTDS possessed inhibitory activity against the mammalian target of rapamycin (mTOR) and also impeded hyper-phosphorylation of Akt as a feedback of inhibition of mTOR by rapamycin.

The apoptotic activity was also observed in primary leukemic blasts, obtained from chronic myelogenous leukemia (CML) patients at onset or from patients in blast crisis and who were imatinib- dasatinib- and nilotinib resistant. These results suggest that these compounds are promising agents for the treatment of leukemia. Due to the fact that the phenomenon of resistance to tyrosine kinases inhibitors (TKIs) remains a major issue in the treatment of patients with CML, the identification of new drugs may be of clinical relevance.

Biography

Gabriella Marfe, female, molecular biologist, graduated from College of Biology, University of Naples "Federico II" in 1982. Actually, she works as researcher for University of Rome "Tor Vergata", Department of Experimental Medicine and Biochemical Sciences, College of Medicine. From 1992-1993, he worked as a visiting scientist for Academisch Ziekenhuis Free university Hospital Amsterdam, Holland, within the project: "Lymphoma in the bb/e rat and identification of myc translocation. From 1994-1995 he worked in as a visiting scientist for University of Tennessee Knoxville. Furthermore, from March 1998, she collaborated within Department of Experimental Medicine and Pathology, University of Rome "La Sapienza" in the laboratory of prof. Marialuisa Lavitrano, regarding the analysis of transgenic pigs. In recent years she focused her study on apoptosis and chronic myelogenous leukemia and got some important success. Actually, she is studying the molecular mechanisms affecting cancer cell sensitivity to PBTDS in hematologic and solid (colon) malignancies.