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Design and Evaluate Anticancer Potential of Haloacetamidines-Dderived PAD4 Inhibitors

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Histones play an important role in human cells by organizing DNA to form basic structural units of chromatin termed nucleosomes. One emerging strategies for cancer treatment is to target enzymes that covalently modify histones thereby regulating cell proliferation and death. For example, histone deacetylase (HDAC) inhibitor, SAHA (also called voriostat or Zolina), has been used successfully in clinical trials and approved by FDA as a monotherapy compound or in combination with various anticancer drugs. We anticipate that our research will offer the chemical and biological groundwork to develop a PAD4 inhibitor for cancer treatment in combination with other anticancer drugs, especially with the HDAC inhibitor SAHA. So the lead compounds, Cl-amidine derivatives were synthesized using a newly designed solution-based method to improve the specificity and bioavailability of the inhibitors. We tested the anticancer activity of the PAD4 inhibitor Cl-amidine and its derivatives and their anticancer activity in combination with the HDAC inhibitor SAHA. Taken together, we identify PAD4 as a promising drug target for cancer treatment, suggesting that epigenetic mechanisms can be explored to develop novel strategies for cancer chemotherapy.