Solid-Phase Parallel Synthesis of Dual Histone Deacetylase-Cyclooxygenase Inhibitors

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Autoren

Luisa M. Bachmann Maria Hanl Felix Feller Laura Sinatra Andrea Schöler **Jens Pietzsch** Markus Laube Finn K. Hansen

Abstract

Multi-target drugs (MTDs) are emerging alternatives to combination therapies. Since both histone deacetylases (HDACs) and cyclooxygenase-2 (COX-2) are known to be overexpressed in several cancer types, we herein report the design, synthesis, and biological evaluation of a library of dual HDAC-COX inhibitors. The designed compounds were synthesized via an efficient parallel synthesis approach using preloaded solid-phase resins. Biological in vitro assays demonstrated that several of the synthesized compounds possess pronounced inhibitory activities against HDAC and COX isoforms. The membrane permeability and inhibition of cellular HDAC activity of selected compounds were confirmed by whole-cell HDAC inhibition assays and immunoblot experiments. The most promising dual inhibitors, C3 and C4, evoked antiproliferative effects in the low micromolar concentration range and caused a significant increase in apoptotic cells. In contrast to previous reports, the simultaneous inhibition of HDAC and COX activity by dual HDAC-COX inhibitors or combination treatments with vorinostat and celecoxib did not result in additive or synergistic anticancer activities.