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Abstract

Synthesis and Biological Evaluation of Novel 3-Isopropenyl-β-Lactams: Heterocyclic Bridged Analogues of Combretastatin A-4 as Novel Antimitotic Agents in Breast Cancer †

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Abstract: Microtubule-targeted drugs are essential chemotherapeutic agents for various types of cancer. We have previously reported the synthesis of 3-vinyl-β-lactams (2-azetidinones) with potent antiproliferative activity against breast cancer MCF-7 cells. As a continuation of our research work on tubulin polymerization inhibitors, we now present the synthesis and biochemical evaluation of a series of novel 3-isopropenyl-β-lactams (2-azetidinones) that are structurally related to the colchicine binding site tubulin inhibitor and vascular targeting agent, Combretastatin A-4. The 3-isopropenyl-β-lactams in this series contain 3,4,5-trimethoxyphenyl ring A (required for CA-4), together with selected ring B substituents. These compounds showed potent activity against breast cancer in MCF-7 and triple negative MDA-MB-231 breast cancer cells and are minimally toxic to non-tumorigenic human embryonic kidney HEK-293T cells. Moreover, the compounds significantly arrested cell division during the G2/M phase and induced apoptosis in the MCF-7 cell line. Immunofluorescence studies in MCF-7 cells showed that the 3-isopropenyl-β-lactam caused mitotic catastrophe by targeting tubulin and inhibited tubulin polymerization. In conclusion, the 3-isopropenyl-2-azetidinones could be promising lead compounds for the development of anti-breast cancer drugs that target tubulin in future clinical trials.

Keywords: combretastatin A-4; MCF-7 cells; β-lactams (2-azetidinones); antimitotic agents

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