Design, Synthesis and Biological Evaluation of a Hybrid Boronic Acid-Quinolinone Derivative as a Novel Acid Ceramidase Inhibitor To Target Breast Cancer

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Breast cancer is one of the most common cancers accounting for 12.5% of all annual new cancer cases worldwide. Overall survival of the patients is limited for aggressive breast cancer phenotypes despite the current treatments. This requires the development of new therapeutics to overcome the disease in a targeted manner. Recently, Acid Ceramidase (AC) emerged as a potential target, overexpressed in various cancer types including breast cancer. In this study, we sought to synthesize a novel drug-like AC inhibitor to target breast cancer. To increase interactions with the target enzyme, we employed a strategy that merges electron donor and electron acceptor groups (quinoline and boronic acid) into a molecule (BFK). Boronic acid’s low cytotoxicity towards healthy cells and wide research on quinoline as a breast cancer inhibitor justify their use. 1H-13CNMR, FTIR, QTOF LC/MS characterization methods were used to validate BFK's structure. RT-PCR verified AC presence in the cell lines we planned to work with. Then, cancerous cells (MCF-7) -along with healthy cells (MCF-10A)- were treated with BFK (0-100 ppm) and cell viability was measured using an ATP dependent viability assay. Cell death was detected using Annexin V/PI staining and cellular apoptosis was biochemically investigated by western blotting. Finally, proteomic analysis quantified the cellular protein CERT, a marker of AC activity. The findings revealed that BFK is a novel, potential drug-like AC inhibitor for targeted breast cancer treatment. Its innovative synthesis approach provides new insights into AC-driven cancer treatment, and could encourage future studies in the field.

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