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Abstract

Combination Therapy Assays with Doxorubicin and Cathepsin L Inhibitors against the Triple-Negative Breast Cancer Line MDA-MB-231 †

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Abstract: Breast cancer is a worldwide health problem as one of the most prevalent types of tumors in the female population. Despite the availability of many therapies, including doxorubicin, novel chemotherapeutic approaches are being studied for this disease, focusing on triple-negative breast cancer cells. Cathepsin L is a cysteine protease that is highly expressed in many tumors, where novel dipeptidyl nitrile inhibitors have been designed and studied over time in our research group. Here, an approach involving the combination therapy of twelve novel cathepsin L inhibitors and doxorubicin was assayed against the triple-negative human breast cancer cell line MDA-MB-231. The cells were cultivated using DMEM medium supplemented with 10% FBS. They were added to 96-plates at a concentration of 1.0×10^4 cells/well. After 24 h of incubation, the medium was removed to add 10 micromolar cathepsin L inhibitors and a range of doxorubicin concentrations (1.0-1 nanomolar). The system was incubated for 72 h before being subjected to MTT assays. The Bliss test was used to evaluate the concentration-dependent assay of these chemicals, which led to synergism for many chemicals. The best combination led to almost 8-times higher potency improvement than doxorubicin alone. The SAR was described for this set of dipeptidyl nitriles. It is not yet known how these chemicals could act in combination, and this is the current focus of our efforts to exploit the biological mechanisms.

Keywords: drug discovery; cell-based assays; combination therapy; in vitro study

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