The Activity of Prospective HSP90 Inhibitors in Breast Cancer Cells

P-06.2-48

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The development of new classes of drugs for cancer therapy is an actual direction of investigation requiring the collaboration of medicine, biology and chemistry. We synthesized a novel class of inhibitors of the molecular chaperon, HSP90. This protein is involved in a proper folding of different proteins in cancer cells including oncogenes. So, it is extremely important to discover new drugs that can disrupt protein folding in cancer cells, which consequently will lead to changes in its metabolism and finally to cell death. Nowadays, several HSP90 inhibitors are used in cancer therapy, but they have some serious disadvantages like complicated synthesis, low efficiency in vivo, and various side effects.

Test compounds were selected by virtual screening their binding affinity to N-domain of HSP90 and synthesized starting from 3-(phenyl)-6,7-dihydrobenzo[d or c]isoxazol-4(5H)-ones by an oximation of them followed by acylation with various carboxylic acids. All breast cancer cell lines were obtained from the ATCC.

We performed screening over than 30 compounds in breast cancer cell lines. We selected the most active drugs and studied their cytotoxicity and effect on different cell signaling cascades. We showed that the inhibitors changed HSP90 intracellular targets levels. It was confirmed by dicrease of Akt, phospho-Akt, Erk1/2 and pNF-κB. We observed the depression of Snail, a key regulator of epithelial-mesenchymal transition. This process initiates metastasis and invasion of tumor cells. Moreover, we noticed that leaders of HSP90 inhibitors had high cytotoxic activity. Cell cycle analysis showed the raised number of apoptotic cells simultaneously without any changes in other phases of the cycle.

A novel class of HSP90 inhibitors could be considered as candidates for further chemical optimization into lead compounds and a preclinical investigation for breast cancer treatment. The reported study was funded by RFBR (project 19-54-04001) and BRFFR (project X19PM-013).

* The authors marked with an asterisk equally contributed to the work.