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Abstract

Development of Synergetic Combinations of a Novel Apoptosis Inducer with AKT and Hsp90 Selective Inhibitors Targeting Hormone-Sensitive and Hormone-Resistant Breast Cancer Cells †

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Introduction: The design and development of antitumor compounds based on an isatin core led to the synthesis of 1-substituted isatin-5-sulfonamides with potent antiproliferative activity. This investigation is aimed at new 1-substituted isatin-5-sulfonamides with pro-apoptotic properties alone and in combination with AKT and Hsp90 inhibitors on hormone-sensitive and hormone-resistant breast cancer cells.

Methods: The synthesis of target 1-substituted isatin-5-sulfonamides involved 3 stages. The alkylation of isatin-5-sulfonamide via various benzyl chlorides allowed us to synthesize previously unknown series of 1-substituted isatin-5-sulfonamides. 4-Hydroxytamoxifen (HT) was used to develop a MCF7-resistant subline (MCF7/HT) via the long-term incubation of MCF7 cells with HT. MCF7 cells were transfected with the p53 luciferase reporter plasmid to obtain MCF7/p53-LUC cells.

Results: 1-(4-((trifluoromethyl)thio)benzyl)isatin-5-sulfonamide (LCTA-3344) exhibited the highest antiproliferative activity, suppressing tumor cells at low micromolar concentrations. After the development of the resistant subline, the IC_{50} values of HT were 5.1 ± 0.3 μM (MCF7) and 10.2 ± 0.4 μM (MCF7/HT), and a resistance index (RI) of 2 was found. Compound LCTA-3344 showed higher antiproliferative activity in MCF7/HT (IC_{50} = 1.4 ± 0.1 μM), than in MCF7 (2.6 ± 0.3 μM). A search for effective combinations with AKT Inhibitor IV (6-(2-benzothiazolyl)-1-ethyl-2-[2-(methylphenylamino)ethenyl]-3-phenyl-1H-benzimidazolium, monoiodide), AKT Inhibitor X (10-DEBC; 2-chloro-N,N-diethyl-10H-phenoxazine-10-butanamine), and Hsp90 Inhibitor (luminespib, NVP-AUY922; 5-[2,4-dihydroxy-5-(1-methylethyl)phenyl]-N-ethyl-4-[4-(4-morpholinylmethyl)phenyl]-3-isoxazolecarboxamide) was performed. The combinations of LCTA-3344 and AKT Inhibitor IV on MCF7 and MCF7/HT were synergetic with combination index (CI) values equal to 0.8 and 0.4 (a higher effect), correspondingly. For comparison, combinations of LCTA-3344 with 10-DEBC and luminespib did not demonstrate such a high effect with a minimal value of CI 0.9. MCF7/p53-LUC cells were used to assess p53 activity. LCTA-3344 did

not increase luciferase activity in MCF7/p53-LUC cells, whereas doxorubicin has been identified as its strong inducer.

Conclusions: A leading 1-substituted isatin-5-sulfonamide LCTA-3344 was 1.9 times more effective against MCF7/HT, than parental cells. The most effective drug combination was LCTA-3344 with AKT Inhibitor IV on the MCF7/HT subline, CI 0.4. The isatin-5-sulfonamide LCTA-3344 induced apoptosis with the p53-independent mechanism, which may provide a basis for novel therapeutic strategies in the treatment of hormone-resistant breast cancers.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/proceedings2024100004/s1, Conference poster.

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