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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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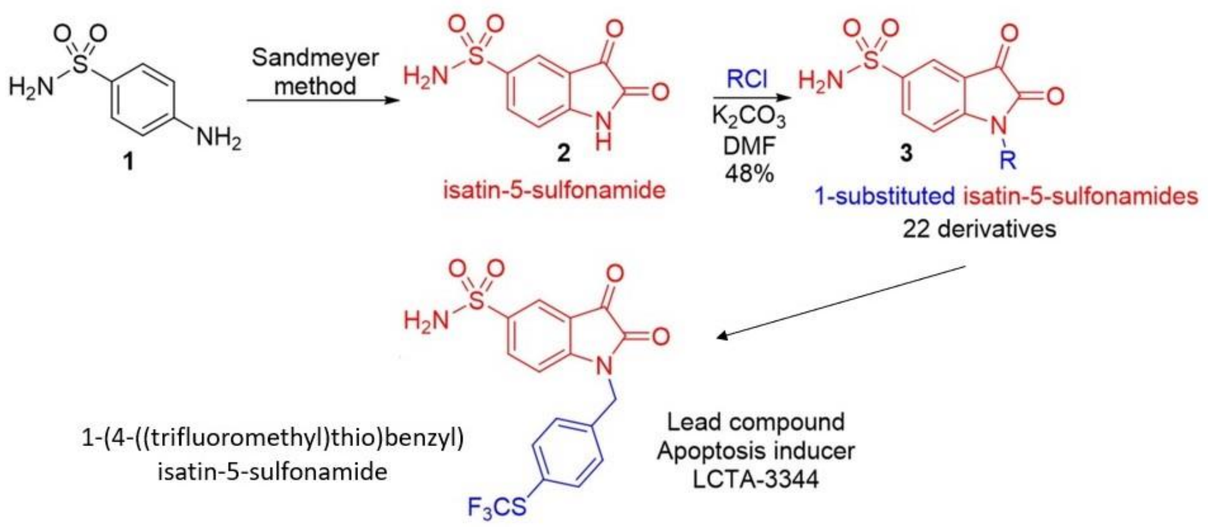
INTRODUCTION & AIM

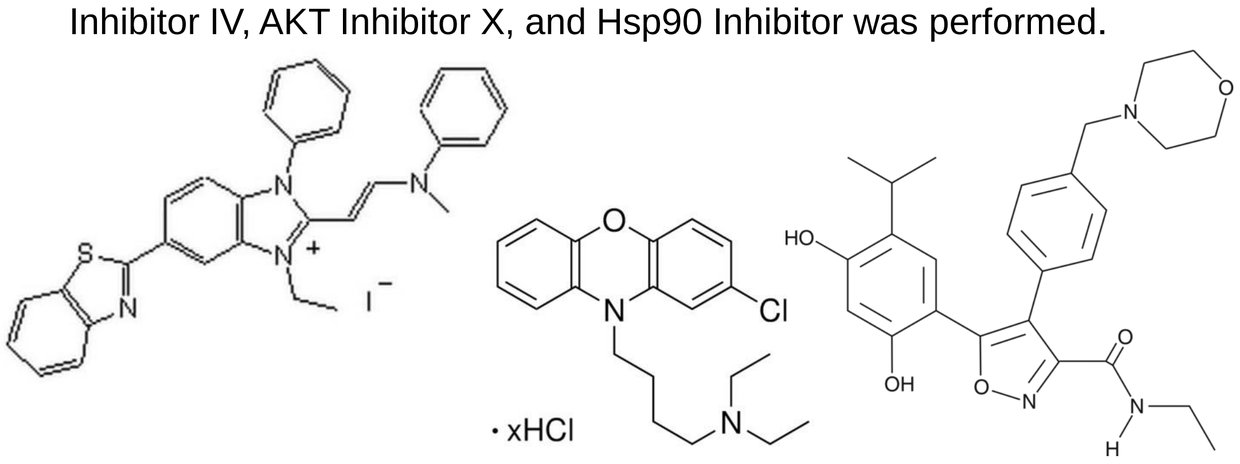
- The design and development of antitumor compounds based on an isatin core led to the synthesis of 1-substituted isatin-5-sulfonamides with potent antiproliferative activity [1].
- This investigation is aimed at new 1-substituted isatin-5-sulfonamides with pro-apoptotic properties alone and in combination with AKT and Hsp90 inhibitors on hormone-sensitive and hormone-resistant breast cancer cells [2].
- **Keywords:** MCF7 breast cancer cell line; isatin-5-sulfonamides; 4-hydroxytamoxifen (HT); AKT Inhibitor IV; antiproliferative effect; resistance; synergism.

METHODS

- The synthesis of 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.



- HT was used to develop a MCF7-resistant subline (MCF7/HT) via the long-term incubation of MCF7 cells with HT.
- The IC_{50} values of HT were 5.1±0.3 μM (MCF7) and 10.2±0.4 μM (MCF7/HT); resistance index of 2 found.
- MCF7 cells were transfected with the p53 luciferase reporter plasmid to obtain MCF7/p53-LUC cells and assess p53 activity.
- A search for effective combinations of the lead compound with AKT Inhibitor IV, AKT Inhibitor X, and Hsp90 Inhibitor was performed.



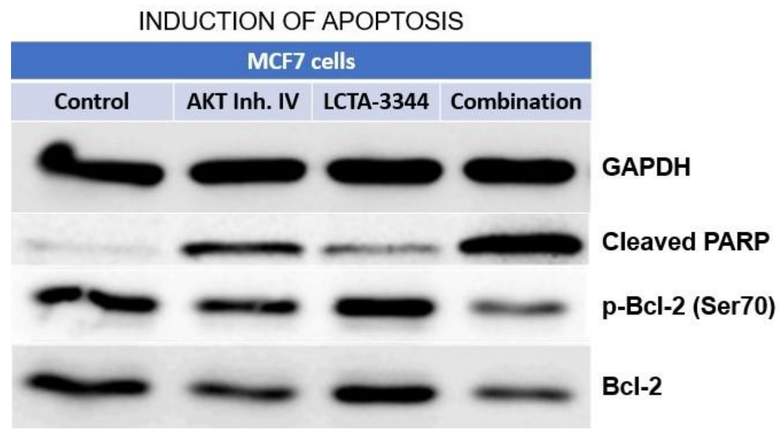
AKT Inhibitor IV (6-(2-benzothiazolyl)-1-ethyl-2-[2-(methylphenylamino) ethenyl]-3-phenyl-1H-benzimidazolium, monoiodide)

AKT Inhibitor X (10-DEBC; 2-chloro-N,N-diethyl-10H-phenoxazine-10-butanamine, hydrochloride)

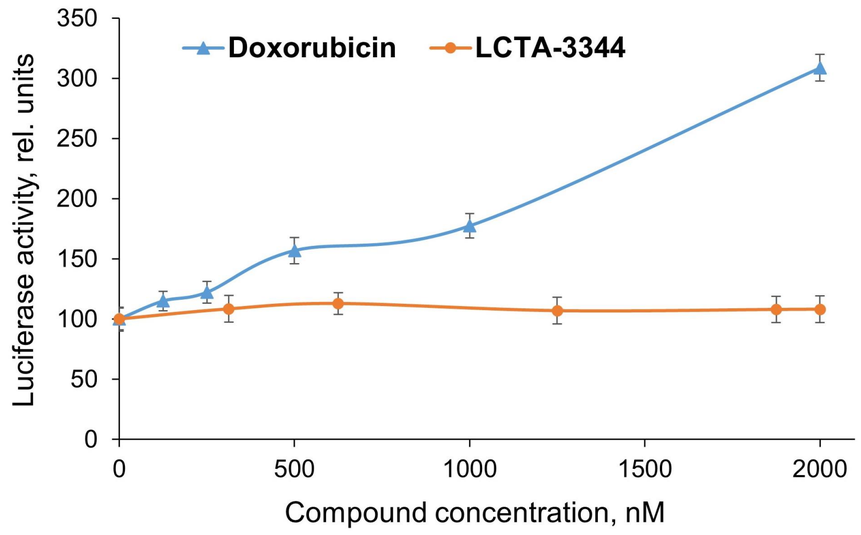
Hsp90 Inhibitor (luminespib, NVP-AUY922; 5-[2,4-dihydroxy-5-(1-methylethyl) phenyl]-N-ethyl-4-[4-(4-morpholinylmethyl)phenyl]-3-isoxazolecarboxamide)

RESULTS & DISCUSSION

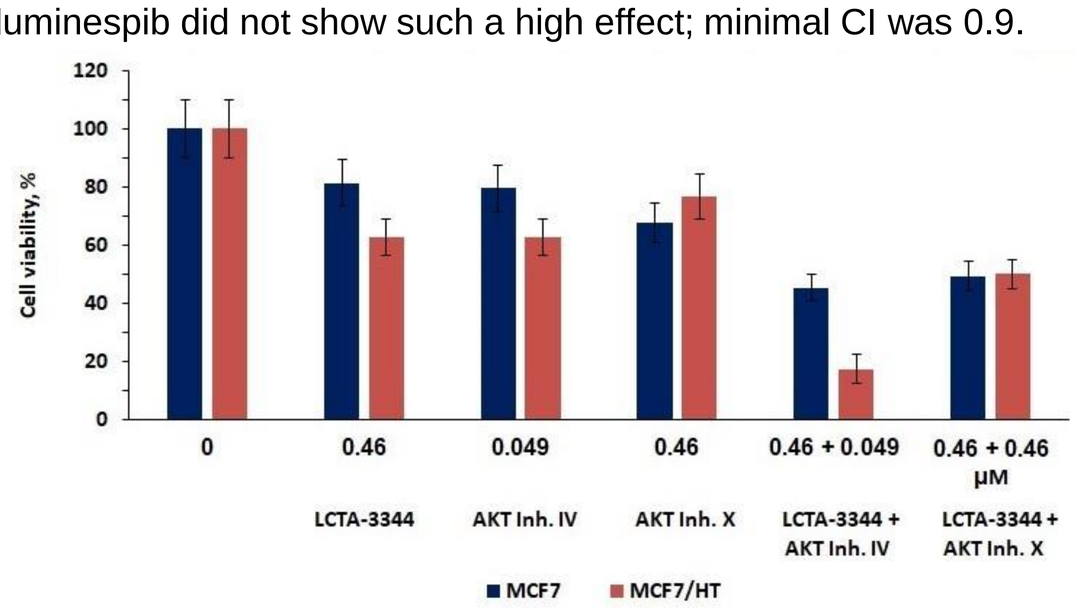
- LCTA-3344 showed the highest antiproliferative activity; the effect was higher in **MCF7/HT (IC_{50}=1.4±0.1 μM), than in MCF7 (2.6±0.3 μM).**
- Apoptosis detected by the PARP cleavage was higher in the presence of AKT Inhibitor IV rather, than LCTA-3344. The combination effect was synergetic. GAPDH was used as a loading control. Bcl-2 was a negative regulator of apoptosis.



- LCTA-3344 did not increase **luciferase activity in MCF7/p53-LUC cells**, whereas doxorubicin has been identified as its strong inducer.



- 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). Combinations with 10-DEBC and luminespib did not show such a high effect; minimal CI was 0.9.



CONCLUSION

- 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.
- LCTA-3344 induced apoptosis with the p53-independent mechanism, which is important in the hormone-resistant breast cancer therapy.
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REFERENCES

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