Novel inhibitors of androgen receptor with antiproliferative potency against hormone-sensitive and hormone-resistant breast cancer cells

#52P

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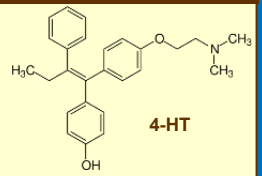
INTRODUCTION

The growth of most types of breast cancer (BC) depends on estrogens. Estrogen binds to estrogen receptor alpha (ERα) and triggers active proliferation in BC cells.
The hormone therapy is aimed at reducing the effect of estrogens on tumor cells and suppressing the rate of tumor growth.
The androgen receptor (AR), another steroid receptor, is a novel possible target in BC cells.
The work aims to develop new selective AR inhibitors with proapoptotic activity.

MATERIALS AND METHODS

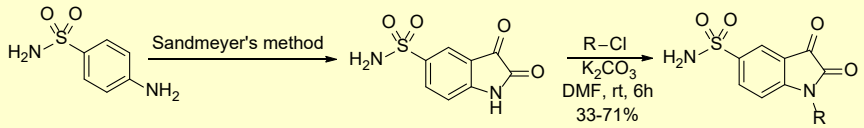
A series of 1-substituted isatine-5-sulfonamides was synthesized applying Sandmeyer's method and subsequent alkylation of the heterocycle moiety by various benzyl chlorides.
The hormone-dependent MCF-7 BC cell line was purchased from American type culture collection (ATCC).
Antiproliferative activity was assessed by the MTT assay.
The hormone-resistant MCF-7/HT subline was obtained by long-term cultivation of MCF-7 cells with the active form of tamoxifen, 4-hydroxytamoxifen (4-HT).
The growth of MCF-7/HT cells was not inhibited by treatment with 10 μM 4-HT.



4-HT

MCF-7 CELLS – AR-POSITIVE BREAST CANCER CELLS

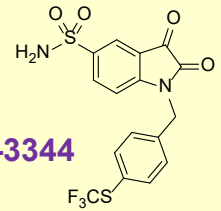
RESULTS



21 examples

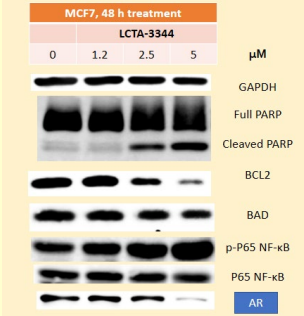
Analysis of antiproliferative activity of new 1-substituted isatin-5-sulfonamides revealed several compounds with low micromolar half-maximal inhibitory concentration (IC_{50}) values.

Compound LCTA-3344 was more active than the reference drug, well-known apoptosis activator 2 (N-(3,4-dichlorobenzyl)isatine).

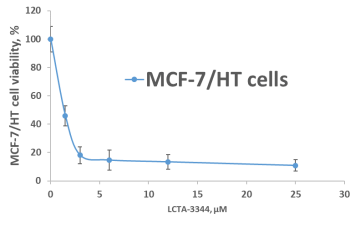


LCTA-3344

IMMUNOBLOTTING RESULTS



- LCTA-3344 significantly blocked AR signaling at a dose of 5 μM.
- LCTA-3344 at micromolar concentrations induced B cell lymphoma 2 (BCL2)-dependent apoptosis in MCF-7 cells.
- GAPDH - glyceraldehyde-3-phosphate dehydrogenase
- PARP - poly (ADP-ribose) polymerase, an apoptotic marker
- BAD - Bcl-2-associated death promoter



LCTA-3344 in concentrations of 0.3-50 μM causes suppression of the growth of hormone-resistant cell subline MCF-7/HT with the IC_{50} value of 1.4 μM. Hormone-resistant cells do not lose their sensitivity to LCTA-3344 and show some increase in comparison with the parent MCF-7 line, for which the IC_{50} value was 2.6 μM.

CONCLUSIONS

- A series of 1-substituted isatin-5-sulfonamides with high activity against hormone-sensitive BC cells was obtained.
- Moreover, LCTA-3344 exhibited antiproliferative effects against hormone-resistant BC cells, induced apoptosis and significantly inhibited the activity of AR.
- Further in-depth investigation of the anticancer properties of LCTA-3344 are in development.

ACKOWLEGEMENTS AND FUNDING

Conflict of interests: nothing to declare. Funding: RSF (agreement 20-13-00402).

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