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Medizinische Chemie



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Frontiers in Medicinal Chemistry

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Major Topics:

- New Antibiotics
- Immunological Diseases
- Endocrine and Intracrine Targets
- New Technologies and Peptides
- Highlights in Medicinal Chemistry



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Antiproliferative Effect of D-Homoestrone Derivatives

Minorics, R., Szeged/H, Bózsity, N., Szeged/H, Mernyák, E., Szeged/H, Zupkó, I., Szeged/H, Schneider, G., Szeged/H, Wölfling, J., Szeged/H

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Although the estrogens have been considered as proliferation-inducing compounds, on the basis of recent experimental results their certain analogues can exert potent antiproliferative effect. One of the most widely investigated compounds is the A-ring modified derivative of estradiol, 2-methoxyestradiol, which has no estrogenic activity.

Our aim was to characterize the mechanism of action of newly synthesized D-ring modified estrone derivatives on female reproductive cancer cell lines. The *in vivo* estrogenic activity of the compounds was also investigated.

The antiproliferative effect of the test compounds was determined on cell-growth inhibition assay. The tumour-selectivity of the most effective compound was established on intact foetal fibroblast cell line (MRC-5). To confirm the apoptosis/necrosis-inducing effect of this compound double fluorescent-staining and FACS analysis were performed under the same experimental conditions. A rat uterotrophic assay was performed to demonstrate the estrogenic activity of the compound.

The antiproliferative effect of the most potent compound ($IC_{50}=5.5 \mu M$ on HeLa cells) was selective to the cancer cell line ($IC_{50}>30 \mu M$ on MRC5 cells). FACS analysis exhibited a substantial increase in G2/M phase after 24 and 48 hours incubation following the degradation of the cells after 72 hours presented by the marked increase of cell number in subG1 phase. The modifications in the cell cycle were also confirmed by morphologic investigations. Our compound exhibited no significant increase in rat uterus weight.

The tested D-homoestrone analogue exerted a potent antiproliferative effect on HeLa cells with no detectable effect via estrogen receptors. Our compound induced cell cycle arrest in the G2/M phase with a subsequent secondary necrosis.