TARGETING ANDROGEN RECEPTOR SPLICE VARIANT 7 IN 22RV1 PROSTATE CANCER CELLS

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BACKGROUND

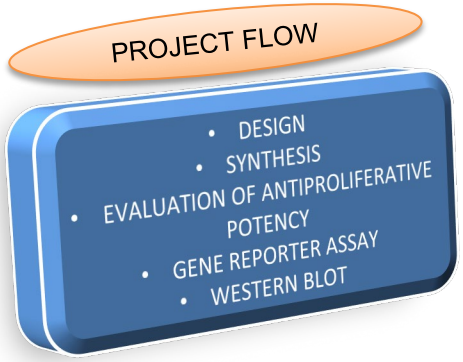
Prostate cancer is the second most frequent men's cancer diagnosis and the fifth leading cause of death worldwide. A large percentage of prostate cancers are initially very sensitive to hormone therapies, but over time the sensitivity to antiandrogens may be lost and cancers can develop resistance through various signalling mechanisms. Expression of the androgen receptor splice variant 7 (AR-V7) in some cases is considered as one of the factors supporting antiandrogen resistance. **The study aims to develop novel AR-V7 inhibitors for prostate cancer therapy.**

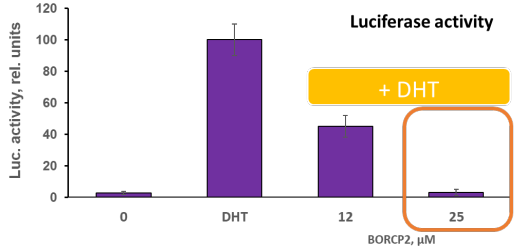
METHODS

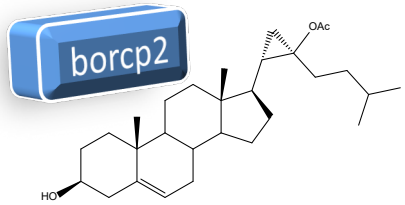
Pregnenolone was used as a starting compound for the preparation of target steroids. Antiproliferative activity was assessed by the MTT test on **22Rv1 cells bearing both AR and AR-V7.** AR activity was assessed using reporter gene analysis. Proteins were analyzed by immunoblotting.

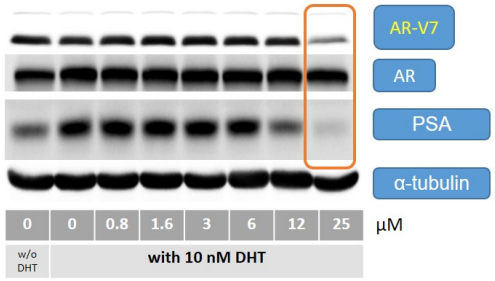
Results

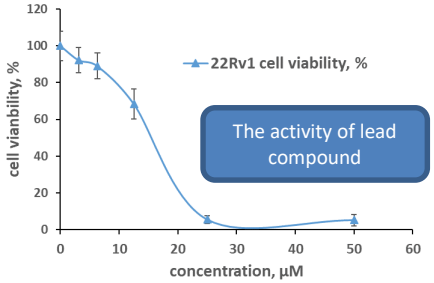
Synthesis of the target compounds included the Kulinkovich reaction of steroid 17-vinyl derivatives with esters. The obtained cyclopropanols were then opened to provide a new series of steroidal delta2-6-ketones with the hydrogen, aryl or alkyl substituent at C-21 and functional groups at C-22 - C-23. Screening for antiproliferative activity revealed the lead compound steroidal cyclopropanol (BORCP2) significantly blocking the growth of 22Rv1 prostate cancer cells. The compound BORCP2 reduced AR activity as determined by gene reporter assay and immunoblotting of PSA. Treatments with steroid BORCP2 resulted in apoptosis and significant decrease in AR-V7 and bcl2 expression in 22Rv1 cells.











CONCLUSIONS

A series of new steroids with high activity against 22Rv1 prostate cancer cells has been obtained. The lead compound effectively inhibited the expression of AR-V7, a form of androgen receptor supporting antiandrogen resistance, and stimulated apoptosis.

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