P74 Synthesis of steroidal oximes and epoxides and its antitumor effect against prostate cancer

Eur Urol Suppl 2019;18(8):e3142

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Introduction & Objectives: Prostate cancer (PCa) is the second most frequently diagnosed type of neoplasm in men with 1.3 million new cases registered in 2018. Currently, several strategies are used to help fight PCa cancer among them the use of antitumor chemotherapy, however, this type of treatment bears several side effects. Steroidal compounds were proven to be efficient against several types of cancer. Epoxides and oximes are two structural features frequently associated with anticancer activity. In this manner, it is our intention to combine these features with the steroidal backbone by synthesizing steroidal epoxides and oximes and evaluating them in a prostate cancer cell line, ultimately to find new anticancer agents with fewer side effects.

Materials & Methods: The compounds 5α-androst-3-en-17-one oxime (3,4 – OLOX), 3α,4α-epoxy-5α-androstan-17-one oxime (3,4 – EPOX), androst-4-en-17-one oxime (4,5 – OLOX) and 4α,5α-epoxyandrostan-17-one oxime (4,5 – EPOX) were synthesized and their cytotoxicity evaluated in a prostate cancer cell line, PC3, at a concentration ranging from 1 to 75 μM . We used the MTT assay to assess cell proliferation, flow cytometry to evaluate viability and types of cell death and fluorescence to measure R.O.S. (reactive oxygen species) production, after treatment of cancer cells with the synthesized compounds. Hemocompatibility was also assessed by haemoglobin release measurement.

Results: The most effective compound in inhibiting tumor cell proliferation was 3,4–OLOX, which demonstrated an IC_{50} value of 13.8 μM. 4,5–OLOX also showed promising results with an IC_{50} of 14.5 μM. The compounds with an epoxide function in the steroidal A-ring did not show any differences comparing to the control. 3,4-OLOX and 4,5-OLOX induced a decrease in cell viability accompanied by an increase in cell death, mainly by apoptosis for 3,4-OLOX and necrosis for 4,5-OLOX. These results are supported by the apoptotic peak observed on cell cycle analysis, as well as, by the increase of BAX/BCL-2 ratio and mitochondrial dysfunction. These alterations are dose-dependent for both compounds. Moreover, ROS levels assessment showed an increase of intracellular peroxides and superoxide anion in cells treated with 3,4–OLOX and 4,5–OLOX compared to non-treated cells. Furthermore, both compounds did not induce haemoglobin release at a concentration of 10 and 75 μM in the hemocompatibility assay.

Conclusions: Preliminary results suggest that 3,4–OLOX and 4,5–OLOX might have an antitumoral effect against P.Ca, mediated by apoptosis and R.O.S. production, which encourages further studies. Compounds were proved to be safe for I.V. administration.

Funding: The authors would like to thank FCT and COMPETE-FEDER for the Strategic Project CNC.IBILI: UID/NEU/04539/2013. The team of CIEPQPF was supported by FCT: UID/EQU/00102/2019. PhD Grant from FCT for IAMarques (SFRH/BD/136973/2018).