IDENTIFICATION OF SPECIFIC ANTAGONISTS FOR THE MEMBRANE RECEPTOR OF ANDROGENS, OXER1 FROM THE ZINC NATURAL PRODUCT DATABASE

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Prostate cancer is known as hormone-sensitive, androgen dependent tumor and the second leading cause of cancer death in men. It is clear that androgens and androgen receptor signaling are crucial for prostate cancer growth and have been exploited therapeutically. However, hormone resistant prostate cancer is an unsolved problem with limited therapeutic choices. The action of androgens is mediated mainly through intracellular androgen receptors, which belong to the nuclear family of receptors. These receptors are transcription factors that determine key cell processes. A recent study by our team identified an alternative androgen receptor on the membrane of prostate cancer cells, OXER1 (5-oxo-6E, 8Z, 11Z, 14Z-eicosatetraenoic acid receptor). Intrestingly, androgens via OXER1 inhibit cancer cell growth and migration. The aim of this research was to identify new molecules that will bind to the membrane receptor of androgens, OXER1 and will have antagonistic effects such as testosterone. To achieve this, we focused on natural products which there were data that may have a pharmacological effect and a therapeutic benefit in prostate cancer. Initially we performed *in silico* studies starting with the modeling of the interaction of OXER1 receptor with testosterone and 5-oxo-ETE. Due to the large number of natural products studied, an algorithm was designed and developed, allowing the fast and accurate classification of the examined chemical molecules. Next, using the advanced bioinformatics tool, OXER1 specific antagonists were identified. *In vitro* verification of the antagonistic properties of the selected compounds was performed in different cellular activities. The identified natural compounds, through bioinformatics methods, were tested in a number of cellular activities, related to the G_{α} and $G_{\beta\gamma}$ activities of OXER1, such as cAMP, actin polymerization and their effect on calcium ion flow. In conclusion, the achievement of the present work is the identification of compounds as specific antagonists of OXER1. All these support that testosterone actions at the membrane level, via OXER1, can provide new targets and agents for possible novel therapeutic approaches in cancer.

Bibliography

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