# TRPM8 ION CHANNEL AS POTENTIAL TARGET FOR CASTRATION RESISTANT PROSTATE CANCER TREATMENT

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TRPM8 has lately emerged as a druggable target in prostate cancer (PC) and TRPM8 modulators have been proposed as potential anticancer agents in this pathology. TRPM8 expression is differentially regulated during prostate carcinogenesis, increasing during the initial stages of the disease and declining after androgen deprivation therapy (ADT). Although TRPM8 expression depends on androgen receptor (AR) transcriptional activity, biochemical findings have reported a direct TRPM8 interaction with androgens or androgen receptor.[1] We recently demonstrated [2] the effectiveness, of our some derivatives, in a castration-resistant prostate cancer (CRPC) model that is usually resistant to androgen deprivation therapy and is considered the most aggressive form of PC. Therefore, the discovery of selective, effective, and potent TRPM8 modulators would improve the molecular arsenal in support of PC standard-of-care treatments. Given our previous results, in the present work we describe the design and the synthesis of a new series of TRPM8 antagonists. To this aim, fluorimetric calcium assays have been used for the preliminary assessment of synthesized compounds potency and selectivity. The preliminary screening allowed the identification of several potent (0.11 μM < $IC_{50}$ < 0.49 μM) and selective compounds. The most potent derivatives were further characterized by patch-clamp electrophysiology assays, confirming their interesting activity. Moreover, the behavior of these compounds was investigated in 2D and 3D models of PC. These TRPM8 antagonists showed remarkable efficacy in inhibiting the growth induced by androgen in various PC cells as well as in CRPC models, confirming their potential as anti-prostate cancer agents. (Figure 1)

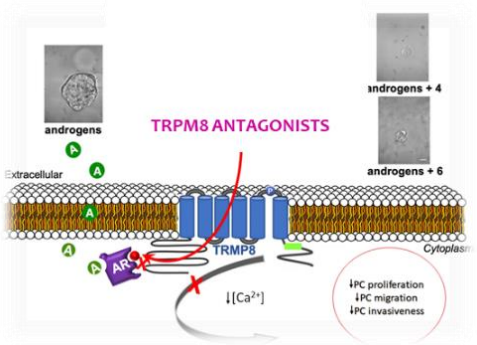


Figure 1. The mechanism of TRPM8 antagonist action in PC cells

**References**

1. Grolez, G. P. et al. Cell Death Dis. 2019,10, 652.
2. Di Donato,M. et al. Sci Rep. 2021 Dec 1;11(1):23232.