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Computational Drug Design: A Multitargeted Approach in Bladder Cancer

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ABSTRACT

Cancer is a complex, robust disease with multiple redundant disease pathways which lead to tumor development, growth, and eventually even death. Despite known redundancies, cancer therapeutics continue to be developed against a single protein target. Initial disease regression occurs followed by relapse in a drug resistant disease state. In response, combinational drug clinical trial targeting multiple pathways began, and have failed due to increased toxicity caused by adverse drug interactions. Development of a single drug that differentially targets multiple disease pathways will result in a more potent therapeutic while inducing minimal toxicity. This was done computationally through in-lab software packages, like CANDOCK, designed to build novel therapeutics that selectively target user defined protein targets. Four protein targets (androgen receptor, estrogen receptor, glucocorticoid receptor, and peroxisome proliferator-activated receptor gamma) were chosen for their known involvement in bladder cancer proliferation and metastasis. Computationally designed compounds were then synthesized and screened for high potency in bladder cancer cell lines using the CellTiter-Blue cell viability assay. Several compounds decreased the cell viability and hindered growth in both mouse and two human bladder cancer cell lines (MB49, T24, and 5637 cell lines, respectively). In addition, some potent compounds displayed decreased nitrous oxide production in RAW 264.7 cells, a mouse macrophage model, using a Griess assay. Thus showing that these compounds could decrease immunosuppression in the tumor microenvironment and slow cancer cell proliferation *in vivo*.

KEYWORDS

Nuclear receptors, multitargeted drugs, bladder cancer, computational drug design