## Identification and Validation of Novel Small Molecule Kinase Antagonists of the PRLR in Breast Cancer for Selective Therapeutic Targeting

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Breast cancer (BC) remains to be a prevalent malignancy, as an estimated 231,840 women were diagnosed in the US in 2015. Furthermore, cancer cells now display chemoresistance towards primary therapeutic methods, necessitating the pursuit of novel innovative targets. Extensive research indicates that prolactin (PRL), an anti-apoptotic hormone in breast cancer acting via the prolactin receptor (PRLR), is associated with enhanced tumor growth, invasiveness, metastasis, and resistance to chemotherapy. Blockade of this receptor could mitigate tumor growth. A multidisciplinary approach combining computational modeling, high-throughput screening, and biology was utilized to identify and validate antagonists of the PRLR in breast cancer from a 340,000 small molecule library. Initially, high-throughput screening and modeling (In-silico docking), along with two biological assays determining Kd (Nb2 rat lymphocytes) and IC50 (BaF3 and T47D BC cell lines) values were utilized to select two molecules, SMI 1 and 6, with high potency and potential to impede the PRLR. To establish validity, the two molecules were further tested for cell invasion (468 BC cell line), protein signaling (T47D BC cell line), cytotoxicity (468 BC cell line), and mitigation of cell cycle progression (Jurkat cell line) using laboratory assays. Laboratory results indicated that SMI 1 and 6 restricted PRLR phosphorylation physically and metabolically, while also halting cell cycle progression, thus preventing breast cancer cell growth. Finally, results illustrated that 1nM concentrations of both inhibitors produced minimal cell death, indicating a possibility for oral drug delivery. Thus, these molecules are the first step to a major cancer drug discovery.