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The Design and Development of GMC1 Analogues: Targeting the Regulation of FKBP52 and Hormonal Receptors in Prostate Cancer Cells

Prostate cancer (PC) is a proliferative disorder characterized by abnormal cell growth that originates in the prostate gland. An effective way of treating castration-resistant PC (CRPC) is androgen deprivation therapy (ADT). Earlier research reported GMC1 effectively inhibits androgen receptor (AR) and glucocorticoid receptor (GR) activities in a variety of PC lines. However, the poor solubility of GMC1 in water and lipid has made it desirable and necessary to design and develop new pharmacophores/analogues with suitable water solubility, liquid stability, and therapeutically potent against CRPC. This study is aimed at designing and developing new analogues of GMC1, and we employed both computational and *in vitro* methods to identify compounds with inhibitory potentials against CRPC related proteins and PC cells. A search of the databases identified over 7000 analogues of GMC1, out of which, 231 were predicted to show better solubility in lipid and water than GMC1. And the results of the molecular docking analysis revealed 27 compounds exhibited higher docking scores toward the FK1 domain of FKBP52 protein compared to the reference drug (FK506) and GMC1. For the AR and GR, 35 and 40 analogues respectively exhibited higher docking scores towards their ligand binding domain (LBD) than the reference drugs (AV6 and RU486, respectively) and GMC1. A further molecular dynamic simulations study of the best docked compounds showed 8, 4 and 7 compounds showed better binding affinities and stable conformation at the binding sites of GR, FKBP52 and AR, respectively. *In vitro* evaluation of the EC_{50} of the identified compounds (25 µM) using luciferase induction assay against AR and GR in MDA cells revealed two compounds, RJ3 and RJ11, showed 45 and 90 % inhibition, respectively. However, the toxicity assay showed the two compounds lowered the reporter's expression. Further identification of lead compounds is under investigation by using in vitro inhibitory activity against MDA cells.