Chronic degenerative diseases (CDDs) pose a significant therapeutic challenge in the health and biomedical sciences due to their multi-faceted and complex nature. CDDs include cancers and neurodegeneration, which can involve complex relationships among genetic and environmental influences compounded by an understanding of the biological pathways implicated in these diseases. This thesis encompasses CDDs identified by multilayered screening pipeline, utilizing cheminformatics and molecular simulations approaches to target key regulatory proteins - GPCRs and kinases in the research presented here. The need for an in-silico approach to CDDs is inherent throughout this research, which includes the use of Quantitative Structure-Activity Relationship (QSAR) modeling, pharmacophore, molecular docking and molecular dynamics simulation, in four separate case studies. The present research has successfully identified promising inhibitors for GPR183, a receptor known to promote malignancies and modulate immune dysfunction, through a cheminformatics-driven pipeline, potential lead molecules for GRK5 to advance potential therapies for neurodegenerative disorders were discovered from machine learning-driven QSAR and pharmacophore modeling. Though a depth of insight presented through a multi-layered framework and integrated use of 2D/3D-QSAR and pharmacophore with extensive molecular dynamics simulations, novel GRK6 inhibitors were identified for multiple myeloma, and insight into the conformational dynamics of the target was also made available. Finally, long time-scale membrane-bound simulations identified potential modulators for GIRK4 channel, a major target for atrial fibrillation. This body of work designed a receptor-specific screening pipeline for CDDs, where work was reasonably expedited and eliminated important workloads of chemistry, thus demonstrating the clear advantage of not only time advantages but the ability of integrating computational methods in pipeline where translation to experimental feasibility can be considered in a measured approach.