Computational Design of PROTACs using Schrödinger Molecular Modeling Tools

Sumati Gurram
Stevens Institute of Technology, Department of Chemistry and Chemical Biology, USA

Aiswarya Mini
Stevens Institute of Technology, Department of Chemistry and Chemical Biology, USA

Abhishek Sharma
Stevens Institute of Technology, Department of Chemistry and Chemical Biology, USA

Abstract:

Breast cancer (BC) is one of the primary cancers that affects women. Taking actions to help prevent the relapse of breast cancer and drug resistance should be a priority. In the past, various therapies have been developed, including Aromatase inhibitors (AIs), Selective Estrogen Receptor Modulators (SERMs), and Selective Estrogen Receptor Degraders (SERDs), which have aided in reducing breast cancer. Building on these therapies, Proteolysis Targeting Chimeras (PROTACs) offer a promising technique that provides targeted protein degradation through the ubiquitin-proteasome system.

This study examines the interactions of seven PROTAC-based ligands, built around palbociclib, an FDA-approved Cyclin-Dependent Kinase (CDK) 4/6 inhibitor. Here, using molecular docking via the Schrödinger Suite, each ligand was evaluated based on its docking score to understand the likelihood of degradation of CDK6. Among these, Ligand 1 showed the lowest docking score (-14.247), indicating the highest potential for CDK6 degradation.