In Silico Identification of selective CDK9 Inhibitors disrupting P-TEFb complex against Triple-Negative Breast Cancer

Rohit Karn[1] and Sanjeev Kumar Singh*[1]
[1]Computer Aided Drug Design and Molecular Modeling Lab,
Department of Bioinformatics, Alagappa University, Karaikudi – 630004
(Email: [1]meetrohitkarn@gmail.com, *skysanjeev@gmail.com)

Abstract

Cyclin-dependent kinase 9 (CDK9) is a regulator of transcription, and its increased activity is associated with worse outcomes in triple-negative breast cancer (TNBC) patients. CDK9 becomes fully active only when it binds with Cyclin T1 to form the P-TEFb complex. Disrupting this interaction offers a way to selectively block CDK9 activity, which can be useful in TNBC therapy. Although more than 100 CDK inhibitors are available for research, there is limited information about their selectivity and off-target effects because most of them are not tested extensively across different CDKs. This gap makes it difficult to identify compounds that specifically inhibit CDK9 without affecting other CDKs that regulate normal cell-cycle functions. To address this, we performed an in-silico evaluation of all the CDK inhibitors that are available in pre-clinical and clinical stages against CDKs 1–13 and examined their effects on their partner cyclins. We focused especially on inhibitors that could disrupt the CDK9–Cyclin T1 interaction. Using virtual screening, docking, protein–protein interaction analysis, and molecular dynamics simulations, we identified compounds with high affinity for CDK9 and low affinity for other CDKs. Compounds were ranked using a delta-value approach based on selectivity. Among the evaluated molecules, Comp44 (CID156492075) showed the highest selectivity for CDK9, followed by Comp224 (CID156011901) and Comp175 (CID145945975). These compounds also reduced the stability of the CDK9–Cyclin T1 complex in MD simulations. Overall, the identified molecules represent promising candidates for selectively targeting CDK9 through disruption of the P-TEFb complex and may contribute to improved therapeutic strategies for TNBC.

Key words: CDK9, P-TEFb, Cyclin T1, TNBC, Selective inhibitors, Molecular dynamics simulation, Protein-Protein interactions.

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