18th National and 3rd International Conference of Iranian Biophysical chemistry

هجدهمین همایش ملی و سومین همایش بین المللی بیوشیمی فیزیک ایران

25-26 Des, 2024, University of Hormozgan

۶-۵ دی ماه ۱۴۰۳، دانشگاه هرمزگان

Potential of Neratinib and Other Compounds as Tyrosine Kinase Inhibitors in Cancer Treatment: Virtual Screening and Molecular Dynamics Analysis

Zohre Ghiasi [*1], Davood Ajloo[2]

1. School of Chemistry, Damghan University, z_ghiasi6822@yahoo.com
2. School of Chemistry, Damghan University, ajloo@du.ac.ir

Abstract

Cancer is a life-threatening ailment characterized by the uncontrolled proliferation of cells. Because cancer is not just a single disease, it is unlikely that there will ever be a single cure for it. At present, no proper therapy is available for the disease, and it is increasing day by day with a high mortality rate. Therefore, the need for drugs to combat this disease has increased. Worldwide collaborative efforts from scientists are underway to determine cancer and reduce mortality rates. Tyrosine kinase inhibitors (TKIs) are widely used in tumor treatment. The screened compounds were followed for SP docking, Extra precision (XP) docking, MM-GBSA analysis, induced-fit (IFD) docking, and MD simulation The absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties of all compounds were analyzed and a final selection was made based on the Lipinski rule of five. Then, ADME/T profiles were determined to validate the pharmacokinetics and pharmacodynamics properties of the hit compounds. the promising ADME properties of the selected compounds emphasize their potential as attractive candidates for cancer treatments. The ligand neratinib revealed the highest docking score of -12.154 kcal/mol. To further validate the interactions of top-scored receptors and ligands, a molecular dynamics study of 4 ns was carried out. This indicated that the protein-ligand complex was stable throughout the simulation period, and minimal backbone fluctuations ensued in the system. Post-MM-GBSA analysis of molecular dynamics data showed a free binding energy of -68.391 kcal/mol. This molecule may emerge as a promising ligand against cancer and thus needs further detailed investigations. These virtual investigations revealed four compounds having binding free energies of − 68.391, − 68.314, − 54.021, and −

51.873 kcal/mol respectively as calculated by the MM-GBSA method. The MD simulation studies confirmed the stability of protein-ligand complexes.

Key words: ADMET, MM-GBSA, molecular dynamics, Molecular docking

References

[1]. Kocarnik J. M, Compton K, Dean F. E. Cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life years for 29 cancer groups from 2010 to 2019: A systematic analysis for the global burden of disease study 2019. JAMA Oncol, 8(3): 420–444, 2022.

[2]. Cardoso E, Guidi M, Blanchet B. Therapeutic drug monitoring of targeted anticancer protein kinase inhibitors in routine clinical use: A critical review. Ther. Drug Monit, 42: 33–44, 2020.

[3]. Ali I. Mukhtar S.D, Hsieh M.F. Facile synthesis of indole heterocyclic compounds based micellar nano anti-cancer drugs. RSC Adv. 8, 37905–37914, 2018.

[4]. Lipinski C.A. Lombardo F. Dominy B.W. Feeney P.J. Experimental and Computational Approaches to Estimate Solubility and Permeability in Drug Discovery and Development Settings. Adv. Drug Deliv. Rev., 64, 4–17.2012.

[5]. Dalal M, Dubey A, Tufail A, Antil N, Sehrawat N, Garg S. Organyltellurium (IV) complexes incorporating Schiff base ligand derived from 2-hydroxy-1-naphthaldehyde: Preparation, spectroscopic investigations, antimicrobial, antioxidant activities, DFT, MESP, NBO, molecular docking, and ADMET evaluation. J Mol Struct 1287:135590, 2023.

[6]. Ylilauri M, Pentikäinen O. MMGBSA as a tool to understand the binding affinities of filamin-peptide interactions, J. Chem. Inf. Model., 53, 2626–2633, 2013.