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In-silico DFT Study, Molecular Docking, ADMET Predictions, and DMS of Isoxazolidine and Isoxazoline Analogs with Anticancer Properties

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Abstract : This study presents a comprehensive analysis of six isoxazolidine and isoxazoline derivatives, leveraging a multifaceted approach that combines Density Functional Theory (DFT), AdmetSAR analysis, and molecular docking simulations to explore their electronic, pharmacokinetic, and anticancer properties. Through DFT analysis, using the B3LYP-D3BJ functional and the 6-311++G(d,p) basis set, we optimized molecular geometries, analyzed vibrational frequencies, and mapped Molecular Electrostatic Potentials (MEP), identifying key sites for electrophilic attacks and hydrogen bonding. Frontier Molecular Orbital (FMO) analysis and Density of States (DOS) plots revealed varying stability levels among the compounds, with 1b, 2b, and 3b showing slightly higher stability. Chemical potential assessments indicated differences in binding affinities, suggesting stronger potential interactions for compounds 1b and 2b. AdmetSAR analysis predicted favorable human intestinal absorption (HIA) rates for all compounds, highlighting compound 3b superior oral effectiveness. Molecular docking and molecular dynamics simulations were conducted on isoxazolidine and 4-isoxazoline derivatives targeting the EGFR receptor (PDB: 1JU6). Molecular docking simulations confirmed the high affinity of these compounds towards the target protein 1JU6, particularly compound 3b, among the isoxazolidine derivatives, compound 3b exhibited the most favorable binding energy, with a g score of -8.50 kcal/mol. Molecular dynamics simulations over 100 nanoseconds demonstrated the stability and potential of compound 3b as a superior candidate for anticancer applications, further supported by structural analyses including RMSD, RMSF, Rg, and SASA values. This study underscores the promising role of compound 3b in anticancer treatments, providing a solid foundation for future drug development and optimization efforts.

Keywords : isoxazolines, DFT, molecular docking, molecular dynamic, ADMET, drugs.
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