Triazole-Benzodiazepine Derivatives: One-Pot Synthesis, Characterization, and Computational Insights

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Abstract

A one-pot regioselective synthesis of triazole-benzodiazepine derivatives was successfully achieved via a [3+2] cycloaddition reaction between 2,3-dihydro-1H-1,5-benzodiazepine and organic azides. The structure of the obtained regioisomer was elucidated by Nuclear Magnetic Resonance (NMR) spectroscopy and confirmed by single-crystal X-ray diffraction of compound 4. Density Functional Theory (DFT) calculations were employed to investigate the electronic structure and reactivity of compound 4. Frontier Molecular Orbital (FMO) analysis revealed a moderate HOMO–LUMO energy gap, suggesting balanced chemical reactivity, while the ionization potential and electron affinity values indicated a marked electrophilic nature. Molecular Electrostatic Potential (MEP) mapping identified nucleophilic regions around the N–N and C=N bonds of the triazole ring and electrophilic zones near the N–H group of the diazepine moiety, suggesting probable sites of non-covalent interactions. Hirshfeld surface analysis provided further insight into the intermolecular contacts and crystal packing features. Moreover, molecular docking and in silico target prediction revealed stable binding supported by various non-covalent interactions. Reduced Density Gradient (RDG) analysis complemented these findings by visualizing weak interactions stabilizing the molecular structure. This combined experimental and theoretical approach provides a comprehensive understanding of the structural, electronic, and interactional properties of triazole-benzodiazepines, highlighting their potential for biological and pharmacological applications.

Keywords

Triazole-Benzodiazepines; Regioselective Synthesis; Density Functional Theory (DFT); Molecular Docking; Corrosion application.