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Abstract

Dynamic Cross-Correlation Matrix (DCCM) Reveals New Insights to Discover New NLRP3 Inhibitors Useful as Anti-Inflammatory Drugs †

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Abstract: The innate immune system is responsible for the body's defense against aggressive agents, mainly through activating pattern-recognition receptors (PRRs). Recognizing these agents results in an inflammatory response that activates tissue repair and eliminates the agent. Among the macromolecules related to these events are inflammasomes (inflammatory response activators), with emphasis on nucleotide-binding domain leucine-rich repeat-containing receptors protein 3 (NLRP3), in which blocking their oligomerization inhibits inflammasome activity. In this way, targeting NLRP3 represents a new approach to designing anti-inflammatory drugs. Here, molecular docking and dynamics, focusing on Dynamic Cross-Correlation Matrix (DCCM) analysis, were used to characterize the significant interactions of MCC950 (known inhibitors) and their analog NP3-166 (ligand co-crystalized) with NLRP3 and generate useful information in drug design. The results showed that the compounds were stable during the MD simulation time (100 ns), demonstrated by the RMSD RMSF, R_g, SASA, and H-bond plots. Analysis of the DCCM graphs showed that more correlated movements are present for MCC950 compared to NP3-166. In fact, the more rigid structure of MCC950 may influence the more significant interaction. A higher correlation observed in both complexes between residues 100–200 and 300–400 highlights the results obtained from the interaction analysis, showing that interaction with Ala^{228} and Arg^{578} may be essential for the inhibitory activity of the compounds. Our findings highlight that greater structural rigidity of the ligand and interactions with residues Ala^{228} and Arg^{578} may be critical for designing new NLRP3 inhibitors with anti-inflammatory potential.

Keywords: NLRP3; DCCM; MD simulations; anti-inflammatory drugs; drug design; molecular modeling; computer-aided drug design; structure-based drug design

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