An Integrated In Silico Workflow for the Design of CNS-Optimized NLRP3 Inhibitors

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The dysregulation of the NLRP3 inflammasome contributes to numerous neurological diseases and neuropsychiatric conditions[1]. NLRP3 is a crucial component of the inflammasome that regulates its activation[2]. Developing small-molecule inhibitors that effectively cross the Blood-Brain Barrier (BBB) remains a significant challenge. This study aims to describe a rational drug design workflow for identifying novel NLRP3 inhibitors presenting optimized Central Nervous System (CNS) profiles.

First, a comprehensive conformational analysis of NLRP3 was performed using available PDB structures to characterize the flexibility of the ATPase NACHT domain, and identify key binding pockets. Based on these templates, a structure-based pharmacophore model was generated, highlighting essential features such as hydrophobic regions, hydrogen bond acceptors, and aromatic interactions.

This pharmacophore model will be used during molecular docking of large chemical libraries to keep relevant binding modes within the active site. CNS-MPO scoring[3] will be used to assess the potential of selected hits to meet physicochemical requirements for BBB penetration.

Overall, this integrated approach is expected to identify promising NLRP3 inhibitor candidates with good potency and optimized CNS drug-like properties.

Bibliography :

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