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From algorithms to action: combatting the neurodegenerative pathology in Parkinson's disease with novel agonists

Parkinson's disease (PD) is the second leading cause of dementia world-wide, characterized by devastating motor and non-motor symptoms. Currently, there is no cure for PD and therapeutics are merely symptomatic based - failing to comprehensively treat the several pathological hallmarks that contribute to the disease's progression. Thus, therapeutic targets capable of regulating the several cellular processes aberrant in PD – such as metabolism, mitochondrial function and inflammation – are of key interest for the treatment of neurodegeneration. Therefore, this study aimed to define the parameters involved in ligand binding to key regulatory proteins for the identification of novel agonists with therapeutic potential. Additionally, it was aimed to investigate the effects of these novel compounds on the neurodegenerative hallmarks in PD cell models. Comprehensive in silico analysis (via induced fit docking and molecular dynamic simulations) led to the discovery of novel compounds W1 and W2 – potential neurodegenerative therapeutics with indicated abilities to activate proteins involved in cellular homeostasis. In vitro investigations confirmed this rise in protein functioning and, notably, the neurodegenerative pathologies of astrocytic PD cell models were significantly decreased when treated with W1 and W2. These results were an undeniable indication of their therapeutic potential. Ultimately, these novel compounds promise to comprehensively combat the neurodegenerative pathology in Parkinson's disease, providing a new therapeutic approach for, not only PD, but neurodegenerative diseases as a whole.

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The design and discovery of small-molecule inhibitors of HIV-1 integrase activity

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