UCZELNIA BADAWCZA
INICJATYWA DOSKONAŁOŚCI

UAM Excellence Visiting Professors

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Exploring the role of orotic acid in DNA aggregation-driven neurodegenerative processes

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sala 2.57 (Sala RW), Wydział Chemii UAM

Wykład w formie tradycyjnej

WYKŁAD ODBYWA SIĘ W RAMACH PROJEKTU

UAM Excellence Visiting Professors (IDUB, POB3)

Abstract: The natural compound orotic acid and its anionic form, orotate, play a pivotal role in various biological processes, serving as essential intermediates in pyrimidine de novo synthesis, with demonstrated connections to dietary, supplement, and neurodrug applications. A novel perspective on biomolecular aggregation at the nanoscale, particularly pertinent to neurodegeneration, challenges the established paradigm positing that peptide (amyloid beta) and protein (tau) aggregation mainly govern the molecular events underlying prevalent neuropathologies. Emerging biological evidence indicates a notable role for G-quadruplex (G4) DNA aggregation in neurodegenerative processes affecting neuronal cells, particularly in the presence of extended (G4C2) n repeats in nuclear DNA sequences. Our study concerns d[(GGGGCC)3GGGG], a G4-forming DNA model featuring G4C2 repeats that is in correlation with neurodegeneration. Through different investigations utilizing spectroscopic techniques (CD, UV, and thermal denaturations), PAGE electrophoresis, and molecular docking, we explored the influence of orotate on the aggregation of this neurodegeneration-associated DNA. A computational approach was employed to construct an in silico model of the DNA aggregate, which involved the docking of multiple G4 units and subsequent integration of the ligand into both the DNA monomer and its in silico aggregated model. The convergence of computational analyses and empirical data collectively supports the hypothesis that orotate possesses the capability to modulate the aggregation of neurodegeneration-related DNA. Notably, the findings suggest the potential utility of orotate as a neurodrug, especially for the therapy of amyotrophic lateral sclerosis (ALS) and Frontotemporal Dementia (FTD), with its current status as a dietary supplement indicating minimal safety issues.

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