Exploring New PKAN Therapies: Current Efforts & Challenges.

Pantothenate Kinase-Associated Neurodegeneration (PKAN) is a devastating neurological disorder with limited therapeutic options. PKAN is caused by mutations in the PANK2 gene, which encodes a critical enzyme involved in the metabolism of coenzyme A (CoA) from vitamin B5. The resulting deficiency in CoA disrupts numerous cellular and metabolic processes, leading to neurodegeneration. In our recent research, we have identified a novel class of compounds, termed VTACs, that demonstrate potent activation of human pantothenate kinase 3 (PANK3) with AC50 values in the nanomolar range. Among these, VTAC1 and VTAC2 have emerged as leading candidates due to their favorable physicochemical properties. Preclinical studies in murine models have revealed that VTAC1 and VTAC2 possess excellent safety profiles and suitable half-lives and penetrate the central nervous system (CNS) effectively, achieving concentrations 2 to 3 times their AC50 values. This presentation will detail the discovery and characterization of VTACs, with a focus on the pharmacokinetic and pharmacodynamic properties of VTAC1 and VTAC2, as well as their safety and efficacy profiles in preclinical models. Our findings suggest that VTAC1 and VTAC2 could represent a significant advancement in the treatment of PKAN, offering hope for patients afflicted by this challenging disease.