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NEDD8 Activating Enzyme E1 Inhibitor TAS4464

National Cancer Institute

Source

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An inhibitor of NEDD8 (neural precursor cell expressed, developmentally down-regulated 8) activating enzyme E1 (NAE), with potential antineoplastic activity. Upon administration, TAS4464 selectively binds to and inhibits NAE, which prevents NAE/NEDD8-mediated signaling and prevents the NEDD8 conjugation of cullin-RING ligase complexes (CRLs). This inactivates the CRLs leading to an accumulation of CRL substrate proteins, such as CDT1, p27, p21 and phosphorylated I κ B, and inactivates nuclear factor-kappaB (NF- κ B) as well as downregulates anti-apoptotic proteins. This causes cell cycle dysregulation, induces apoptosis, and inhibits tumor cell proliferation and survival. NAE catalyzes the first step in the NEDD8 conjugation (neddylation) pathway which controls cancer cell growth and survival through activation of CRLs.