EED Inhibitor MAK683

National Cancer Institute

Source

National Cancer Institute. EED Inhibitor MAK683. NCI Thesaurus. Code C133819.

An inhibitor of embryonic ectoderm development protein (EED) and allosteric inhibitor of polycomb repressive complex 2 (PRC2), with potential antineoplastic activity. Upon administration, MAK683 selectively binds to the domain of EED that interacts with trimethylated lysine 27 on histone 3 (H3K27me3), which leads to a conformational change in the EED H3K27me3-binding pocket and prevents the interaction of EED with the histone methyltransferase enhancer zeste homolog 2 (EZH2). Disruption of the EED-EZH2 protein-protein interaction (PPI) results in a loss of H3K27me3-stimulated PRC2 activity and prevents H3K27 trimethylation. This decrease in histone methylation alters gene expression patterns associated with cancer pathways and results in decreased tumor cell proliferation in EZH2-mutated and PRC2-dependent cancer cells. PRC2, a histone H3 lysine 27 methyltransferase and multi-protein complex comprised of EZH2, EED and suppressor of zeste 12 (SUZ12), plays a key role in gene regulation, especially during embryonic development. EZH2, the catalytic subunit of PRC2, is overexpressed or mutated in a variety of cancer cells. EED is essential for the histone methyltransferase activity of PRC2 because EED directly binds to H3K27me3.