

Mixed Lineage Kinase (MLK) Inhibitors and Methods of Use

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Technology description

Brief Description:

Mixed lineage kinases (MLKs) are MAPK kinase kinases that target JNK and p38 MAPK for activation in response to diverse stimuli that stress cells. As a result, the MLKs regulate a broad range of cellular processes. MLK3 is the most widely expressed MLK family member and is present in neurons. It is activated by GTPases of the Ras superfamily, such as Cdc42 and Rac, which trigger protein dimerization via a leucine zipper interface, resulting in auto-phosphorylation at Thr277 and Ser281 within the protein activation loop and subsequent activation of the enzyme.

Application area

MLKs are implicated in a wide range of human diseases, particularly neuronal diseases such as Parkinson's disease, Alzheimer's disease, HIV associated neurocognitive disorder, traumatic brain injury and stroke. While MLK inhibitors hold great promise in the treatment of a variety of neuronal conditions, exploration of the use of these compounds has been hampered due to a lack of small molecule MLK3 inhibitors with improved pharmacokinetic and brain penetrating properties.

Advantages

The University of Rochester has filed patents on several novel small molecule inhibitors of MLKs. These compounds are currently undergoing pre-clinical testing and show an ability to cross the blood:brain barrier. Ongoing research continues to show that several of these molecules are biologically effective at inhibiting the activity of MLKs.

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