U0126

The compound U0126 (1,4-diamino-2,3-dicyano-1, 4-bis[2-aminophenylthio]butadiene) was identified as an inhibitor of AP-1 transactivation in a cell-based reporter assay. U0126 was also shown to inhibit endogenous promoters containing AP-1 response elements but did not affect genes lacking an AP-1 response element in their promoters. These effects of U0126 result from direct inhibition of the mitogen-activated protein kinase kinase family members, MEK-1 and MEK-2. Inhibition is selective for MEK-1 and -2, as U0126 shows little, if any, effect on the kinase activities of protein kinase C, Abl, Raf, MEKK, ERK, JNK, MKK-3, MKK-4/SEK, MKK-6, Cdk2, or Cdk4. Comparative kinetic analysis of U0126 and the MEK inhibitor PD098059 (Dudley, D. T., Pang, L., Decker, S. J., Bridges, A. J., and Saltiel, A. R. (1995) Proc. Natl. Acad. Sci U. S. A. 92, 7686-7689) demonstrates that U0126 and PD098059 are noncompetitive inhibitors with respect to both MEK substrates, ATP and ERK. We further demonstrate that the two compounds bind to deltaN3-S218E/S222D MEK in a mutually exclusive fashion, suggesting that they may share a common or overlapping binding site(s). Quantitative evaluation of the steady state kinetics of MEK inhibition by these compounds reveals that U0126 has approximately 100-fold higher affinity for deltaN3-S218E/S222D MEK than does PD098059. We further tested the effects of these compounds on the activity of wild type MEK isolated after activation from stimulated cells. Surprisingly, we observe a significant diminution in affinity of both compounds for wild type MEK as compared with the deltaN3-S218E/S222D mutant enzyme. These results suggest that the affinity of both compounds is mediated by subtle conformational differences between the two activated MEK forms. The MEK affinity of U0126, its selectivity for MEK over other kinases, and its cellular efficacy suggest that this compound will serve as a powerful tool for in vitro and cellular investigations of mitogen-activated protein kinase-mediated signal transduction [1)].

U0126 is a highly selective inhibitor of both MEK1 and MEK2, a type of MAPK/ERK kinase.

U0126 was found to functionally antagonize AP-1 transcriptional activity via noncompetitive inhibition of the dual specificity kinase MEK with IC50 of 72 nM for MEK1 and 58 nM for MEK2. U0126 inhibited anchorage-independent growth of Ki-ras-transformed rat fibroblasts by simultaneously blocking both extracellular signal-regulated kinase (ERK) and mammalian target of rapamycin (mTOR)-p70(S6K) pathways.

The effects of U0126 on the growth of eight human breast cancer cell lines shown that U0126 selectively repressed anchorage-independent growth of MDA-MB231 and HBC4 cells, two lines with constitutively activated ERK.

Loss of contact with substratum triggers apoptosis in many normal cell types, a phenomenon termed anoikis. U0126 sensitized MDA-MB231 and HBC4 to anoikis, i.e., upon treatment with U0126, cells deprived of anchorage entered apoptosis.

U0126 is also a weak inhibitor of PKC, Raf, ERK, JNK, MEKK, MKK-3, MKK-4/SEK, MKK-6, Cdk2 and Cdk4.

Its potential for wiping long-term memories in rats has been studied at the Center for Neural Science at New York University.

Treatment with the MEK inhibitor U0126 inhibited the activation by TCF7L2 or EGR1 overexpression. Moreover, overexpression of TCF7L2 or EGR1 accelerated the migration and invasion of ESCC cells. A

synergistic effect was observed between TCF7L2 and EGR1 in amplifying the induction of LCN2 and enhancing migration and invasion. Taken together, our study indicates that TCF7L2 and EGR1 are the KTAPs of LCN2, within a positive “LCN2→MEK/ERK→LCN2” path, to promote the migration and invasion of ESCC cells. Based on their clinicopathological significance, LCN2 and its two expression regulators TCF7L2 and ERG1 might be therapeutic targets for ESCC [2].

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2)
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