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PERK Inhibitor II, GSK2656157 - Calbiochem A cell-permeable, potent, ATP-competitive inhibitor of EIF2AK3/PERK (IC?? = 0.9 nM)

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Description

A cell-permeable pyrrolopyrimidinamine compound that acts as a potent, ATP-competitive EIF2AK3/PERK inhibitor (IC50 = 0.9 nM, [ATP] = 10 &#181,M), displaying >=511-fold selectivity over HRI/EIF2AK1, BRK, PKR/EIF2AK2, and MEKK2 (IC50 = 460, 822, 905, and 954 nM, respectively) and much reduced or little activity toward more than 300 other kinases. While GSK2656157 potently inhibits ER stress-induced enhancement of PERK and eIF2alpha phosphorylation as well as ATF4 & CHOP upregulation in human PxBC3 and murine LL/2 cultures in vitro (IC50 <=30 nM, 1 h drug preincubation prior to 6 h ER-stress induction by 1 &#181,M Thapsigargin, Cat. No. 586005), only basal PERK phosphorylation, but not basal eIF2alpha phosphorylation or ATF4 & CHOP expression, is seen inhibited in pancreas (by >95% up to 8 h post single 50 mg/kg oral dose) and tumor tissues upon GSK2656157 administration in mice in vivo, resulting in the observed antitumor efficacy (54-110% tumor growth inhibition, 150 mg/kg/12 h via p.o.) and reversible pancreas damage (44% and 95% of control pancreas mass, respectively, 1 d and 15 d post 14 d 150 mg/kg/12 h oral dosing). Comparing to its structural analog GSK2606414 (Cat. No. 516535), GSK2656157 exhibits much reduced potency toward Aurora B, MLK2/MAP3K10, MLCK2/MYLK2, c-MER (IC50 = 1.259, 2.796, 3.039, and 3.431 &#181,M, respectively), c-Kit, and DDR2 (69.84% and 25.41% inhibition, respectively, at 10 &#181,M), A cell-permeable pyrrolopyrimidinamine compound that acts as a potent, ATP-competitive EIF2AK3/PERK inhibitor (IC50 = 0.9 nM, [ATP] = 10 &#181,M), displaying >=511-fold selectivity over HRI/EIF2AK1, BRK, PKR/EIF2AK2, and MEKK2 (IC50 = 460, 822, 905, and 954 nM, respectively) and much reduced or little activity toward more than 300 other kinases. Potently prevents ER stress-induced enhancement of PERK and eIF2alpha phosphorylation as well as ATF4 & CHOP upregulation in human BxPC3 and murine LL/2 cultures in vitro (IC50 <=30 nM, 1 h drug preincubation prior to 6 h 1 &#181,M Thapsigargin treatment, Cat. No. 586005) and exhibits antitumor efficacy against 3 pancreas and 1 multiple myeloma xenografts in mice (54-110% tumor growth inhibition, 150 mg/kg/12 h via p.o.) in vivo. More selective than GSK2606414 (Cat. No. 516535).