Product Data Sheet

Product Name: Bay 65-1942 free base
Cat. No.: GC35474

Chemical Properties

Cas. No.	600734-02-9		
SMILES	O=C1OCC2=C([C@H]3CNCCC3)C=C(C4=C(O)C=CC=C4OCC5CC5)N=C2N1		
Formula	$C_{22}H_{25}N_3O_4$	M.Wt	395.45
Solubility	Soluble in DMSO	Storage	Store at -20°C
General tips	For obtaining a higher solubility , please warm the tube at 37 ℃ and shake it in the ultrasonic bath for a while.Stock solution can be stored below -20℃ for several months.		
Shipping Condition	Evaluation sample solution : ship with blue ice All other available size: ship with RT , or blue ice upon request.		
Structure	Bay 65-1942 free base		

Protocol

Cell experiment: Cell viability is determined by seeding MYL-R cells on a 96-well plate at 4×104 cells/well in 100 µL RPMI growth medium supplemented with kinase inhibitors. Growth media and kinase inhibitors are replenished at 24 hours, and at 48 hours. 20 µL of MTS assay reagent is added to each well. The plate is returned to the incubator for approximately 1 hour and the absorbance at 490 nm is recorded. For combination index (CI) experiments, cells are grown and assayed. To determine AZD6244 and BAY 65-1942 (10 µM) dose-effects, cells are treated with a series of three-fold dilutions of each drug singly, or in combination while maintaining a constant ratio of 1:2, respectively. Cell viability results are analyzed to derive CI values. The CI values from three independent experiments are averaged[2].

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Animal experiment:

Mice[1]Male C57BL/6 mice, 8-10 wk of age are used. To investigate IKKβ inhibition in myocardial IR injury, mice are subjected to 30 min of cardiac ischemia followed by varying periods of reperfusion. An intraperitoneal injection of Bay 65-1942 (5 mg/kg) at appropriate dosing time points is administered. Nontreatment groups receive a vehicle of 10% cremaphor in water. In treatment groups, Bay 65-1942 is delivered either prior to ischemia, at the time of reperfusion, or 2 h after reperfusion injury. Infarct size is measured 24 h after reperfusion injury in sham, vehicle, and each treatment group. To confirm myocardial injury, serum creatine kinase-muscle-brain fraction (CK-MB) levels are measured 1 h after reperfusion in animals pretreated with Bay 65-1942.

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References:

[1]. Moss NC, et al. IKKbeta inhibition attenuates myocardial injury and dysfunction following acute ischemia-reperfusion injury. Am J Physiol Heart Circ Physiol. 2007 Oct;293(4):H2248-53.
[2]. Cooper MJ, et al. Application of multiplexed kinase inhibitor beads to study kinome adaptations in drug-resistant leukemia. PLoS One. 2013 Jun 24;8(6):e66755.

Background

Bay 65-1942 free base is an ATP-competitive and selective IKKβ inhibitor. IKKβ

Delivery of Bay 65-1942 prior to ischemia significantly decreases left ventricular infarct size compared with animals receiving vehicle. Compared with sham animals, animals receiving vehicle have a significant increase in the infarct-to-area at risk (AAR) ratio (70.7±3.4 vs. 5.8±3.4%, P<0.05). This ratio is significantly reduced by treatment with

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Bay 65-1942 at each time point (prior to ischemia 42.7±4.1%, at reperfusion 42.7±7.5%, 2 h of reperfusion 29.4±5.2%; each group P<0.05 vs. vehicle). Animals pretreated with Bay 65-1942 (n=3) have significantly attenuated CK-MB levels compared with those animals without treatment prior to IR (14,170 ±3,219 units, P<0.05 vs. vehicle)[1].

Inhibitors of MEK (AZD6244) and IKK (BAY 65-1942) are used at their IC50 concentrations, as determined by a 48 hour MTS assay, which achieve sufficient inhibition of kinase activity. MYL-R cells are treated for 24 hours with AZD6244 (5 μM), BAY 65-1942 (10 μM), or a combination of these inhibitors at the same concentrations. AZD6244 and BAY 65-1942 demonstrate synergistic inhibition of cell viability at the dose combination (5 μM AZD6244+10 μM BAY 65-1942), which correlates with IC75 (CI = 0.48±0.01). Synergism is also indicated at the IC50 (CI = 0.56±0.09) and IC90 (CI = 0.46±0.02) dose combinations reported by the software (CI values are the mean of three independent experiments, ± standard deviation). AZD6244 and BAY 65-1942 treatment induces 2- and 1.3-fold caspase 3/7 activation, respectively, compared to the DMSO-treated cells. Treatment with a combination of AZD6244 plus BAY 65-1942 leads to a 3.2-fold increase in caspase 3/7 activity[2].

[1]. Moss NC, et al. IKKbeta inhibition attenuates myocardial injury and dysfunction following acute ischemia-reperfusion injury. Am J Physiol Heart Circ Physiol. 2007 Oct;293(4):H2248-53. [2]. Cooper MJ, et al. Application of multiplexed kinase inhibitor beads to study kinome adaptations in drug-resistant leukemia. PLoS One. 2013 Jun 24;8(6):e66755.

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