SB-216763

Product Number S3442
Storage Temperature at -20 °C

Cas #: 280744-09-4
Synonyms: 3-(2,4-Dichlorophenyl)-4-(1-methyl-1H-indol-3-yl)-1H-pyrrole-2,5-dione

Product Description
Molecular Formula: C_{19}H_{12}N_{2}O_{2}Cl_{2}
Molecular Weight: 371.2
Appearance: orange solid
Purity: >99% by HPLC

Glycogen synthase kinase-3 (GSK-3) is a serine/threonine protein kinase that exists as two isozymes, GSK-3\(\alpha\) and GSK-3\(\beta\), with molecular weights of 51 and 46 kDa, respectively. Insulin and certain growth factors, such as NGF and GDNF, activate phosphatidylinositol 3-kinase (PI3-K) and its downstream effector protein kinase B (PKB; also known as Akt), which in turn phosphorylates and inactivates GSK-3. Inhibition of GSK-3 promotes survival of central and peripheral neurons, stabilizes cytoplasmic \(\beta\)-catenin levels, reduces GSK-3-dependent tau phosphorylation, and has been postulated as a site of action for lithium in the treatment of bipolar disorder.\(^1\)

In the search for potent and selective GSK-3 inhibitors, a series of maleimides was synthesized and evaluated against human GSK-3\(\alpha\) and \(\beta\). SB-216763 is a structurally distinct maleimide that inhibits GSK-3\(\alpha\) in vitro in an ATP competitive manner with an IC\(_{50}\) value of 34 nM.\(^2\) It also inhibits GSK-3\(\beta\) with similar potency, which confirms the high degree of homology of the ATP binding site within the isozymes.\(^1,2\) The selectivity for GSK-3 was established by testing SB-216763 against a panel of 24 protein kinases, including PKB and 3-phosphoinositide-dependent protein kinase-1 (PDK-1). None of the kinases were inhibited by SB-216763 at concentrations that caused significant inhibition of GSK-3.\(^1\)

SB-216763 reduces neuronal cell death in cerebellar granule neurons in vitro in a concentration-dependent manner, as measured by the Thiazolyl Blue Tetrazolium Bromide (MTT) cell proliferation assay. Maximal neuroprotection is achieved at 3 \(\mu\)M.\(^2\) This compound mediated promotion of neuronal survival correlates with the suppression of apoptosis as confirmed by the detection of enriched mono- and oligonucleosomes in apoptotic cells by ELISA.

SB-216763 also increases cytoplasmic \(\beta\)-catenin levels and reduces GSK-3-dependent tau phosphorylation.\(^2,3\)

As is the case for insulin, SB-216763 reduces phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase) gluconeogenic gene expression in a dose-dependent manner. These results indicate that SB-216763 may alleviate hyperglycemia via increased glycogen synthesis, even in insulin-resistant cells.\(^4\)

Preparation Instructions
SB-216763 is soluble in DMSO at 20 mg/ml. It is insoluble in water.

Storage/Stability
Store SB-216763 at –20 °C tightly sealed.

Sold for research purposes under agreement from GlaxoSmithKline

References