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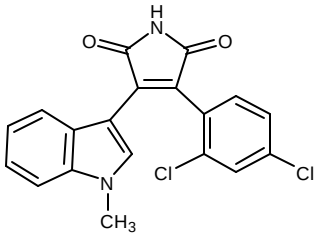
ProductInformation

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: $C_{19}H_{12}N_2O_2Cl_2$
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-3α and GSK-3β, 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-3α promotes survival of central and peripheral neurons, stabilizes cytoplasmic β-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-3α and β. SB-216763 is a structurally distinct maleimide that inhibits GSK-3α *in vitro* in an ATP competitive manner with an IC_{50} value of 34 nM.[2] It also inhibits GSK-3β 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 μM.[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 β-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
1. Smith, D.G., et al., 3-Anilino-4-arylmaleimides: potent and selective inhibitors of glycogen synthase kinase-3 (GSK-3). Bioorg. Med. Chem. Lett., **11**, 635-639 (2001).
2. Cross, D. A., et al., Selective small-molecule inhibitors of glycogen synthase kinase-3 activity protect primary neurones from death. J. Neurochem., **77,** 94-102 (2001).

3. Coghlan, M.P., et al., Selective small molecule inhibitors of glycogen synthase kinase-3 modulate glycogen metabolism and gene transcription. Chem. Biol., **7**, 793-803 (2000).

4. Lochhead, P.L., et al., Inhibition of GSK-3 selectively reduces glucose-6-phosphatase and phosphatase and phosphoenolypyruvate carboxykinase gene expression. Diabetes, **50**, 937-946 (2001). AH 04/03