

New Product Highlights

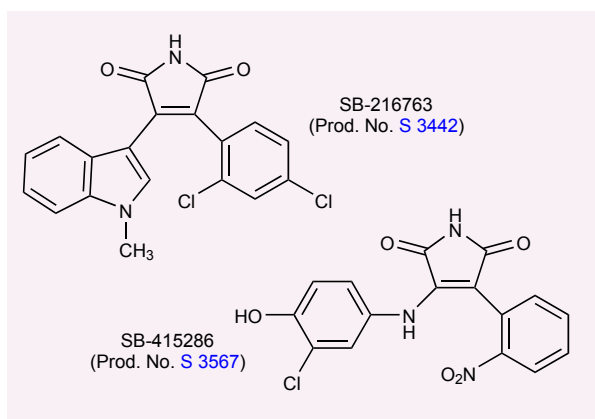
SB-216763 and SB-415286: Novel, potent and selective glycogen synthase kinase-3 (GSK-3) inhibitors

Glycogen synthase kinase-3 (GSK-3) is a serine/threonine protein kinase that exists as two isozymes referred to as α and β (Prod. No. [G 1663](#)). Their catalytic domains (ATP-binding site) have about 90% identity, but the amino terminal region of GSK-3 α has approximately 60 additional amino acid residues. The differences in function between the isozymes have yet to be established [1]. GSK-3 is a principal physiological substrate of protein kinase B (PKB; also known as Akt) and the activity of GSK-3 is inhibited by PKB/Akt-mediated phosphorylation in response to growth factor stimulation [1-3]. **Insulin** (Prod. No. [I 5500](#)) and certain growth factors, such as **nerve growth factor** (NGF, Prod. No. [N 1408](#)) and **glial-derived neurotrophic factor** (GDNF, Prod. No. [G 1777](#)), activate **phosphatidylinositol 3-kinase** (PI3K, Prod. No. [P 8615](#)) and its downstream effector PKB, which in turn phosphorylates and inactivates GSK-3. Inhibition of GSK-3 leads to the modulation of multiple GSK-3 regulated cellular processes including glycogen synthesis in skeletal muscle [4], neuronal cell survival [2] and alleviation of hyperglycemia via increased glycogen synthesis, even in insulin-resistant cells [3,4].

Sigma-RBI is pleased to offer two novel, potent and selective cell-permeable inhibitors of GSK-3, **SB-216763** (Prod. No. [S 3442](#)) and **SB-415286** (Prod. No. [S 3567](#)). Both compounds inhibit GSK-3 α activity with IC₅₀ values of 34 and 78 nM, respectively, and show similar potency towards purified GSK-3 β [1-3]. Each compound specifically inhibits GSK-3 with no significant activity towards a panel of 24 other protein kinases, including PKB, PDK1 and CDK-2 [1-3]. In addition, both compounds potently promote survival of central and peripheral neurons in culture in a concentration-dependent manner following treatment

with the PI3K inhibitor **LY-294,002** (Prod. No. [L 9908](#)) or potassium withdrawal, as measured by **thiazolyl blue tetrazolium bromide** (MTT, Prod. No. [M 2128](#)) assay. Maximal neuroprotection was observed with 3 μ M SB-216763 or 30 μ M SB-415286 [2]. Furthermore, both compounds inhibit expression of the glucose-6-phosphatase (G6Pase) and phosphoenolpyruvate carboxykinase (PEPCK) genes, which leads to increased glycogen synthesis [3,4].

SB-216763 and SB-415286 will prove to be useful tools in studying both the PKB/Akt pathway and GSK-3 regulated processes.



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References

1. Smith, D.G., et al., *Bioorg. Med. Chem. Lett.*, **11**, 635-639 (2001).
2. Cross, D.A., et al., *J. Neurochem.*, **77**, 94-102 (2001).
3. Coghlan, M.P., et al., *Chem. Biol.*, **7**, 793-803 (2000).
4. Lochhead, P.L., et al., *Diabetes*, **50**, 937-946 (2001).

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