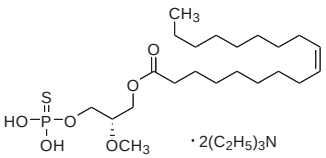
OMPT: Subtype selective lysophosphatidic acid (LPA_3) receptor agonist

Available First from Sigma-RBI

Prod. No. **O 2514**



Lysophosphatidic acid (LPA; **L 7260**), a bioactive lysophospholipid mediator that acts via three G protein-coupled receptors, LPA_1, LPA_2 and LPA_3, has been shown to elicit a wide spectrum of biological responses including stimulation of cell proliferation, cell survival, platelet aggregation, smooth muscle cell contraction, and tumor cell invasion [1]. Accordingly, LPA has been implicated in a variety of pathophysiological conditions including cardiovascular and neoplastic diseases as well as certain types of cancer [1]. An understanding of the functional significance of LPA signaling pathways has been hampered by the absence of LPA receptor subtype-selective agonists and antagonists. However, an ester-linked thiophosphate derivative of LPA, referred to as OMPT (1-oleoyl-2-*O*-methyl-*rac*-glycero-phosphothionate) has recently been described as a selective agonist at the LPA_3 receptor.

At concentrations <100 nM, OMPT induced increases in intracellular [Ca^{2+}] in LPA_3 receptor-expressing Sf9 cells, but not in LPA_2 receptor-expressing cells [2]. Moreover, using a GTP[γ-^{35}S] cell membrane binding assay, OMPT was shown to stimulate LPA_3 receptor-transfected HEK293T cells with an EC_{50} value of 276 nM, while exhibiting no activity at LPA_1 receptors and only weak agonist activity at concentrations >1 mM in LPA_2 transfected cells [2]. For comparison, EC_{50} values for LPA in the same systems were 196, 128, and 27 nM, respectively [2].

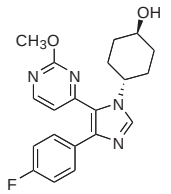
OMPT will therefore serve as a powerful tool for elucidating the role of the LPA_3 receptor versus LPA_1 and LPA_2 receptors in LPA-mediated cell signaling events.

References

1. Moolenaar, W.H., LPA: a novel lipid mediator with diverse biological actions., *Trends Cell Biol.*, **4**, 213-219 (1994).
2. Hasegawa, Y., et al., Identification of a phosphothionate analogue of lysophosphatidic acid as a selective agonist of the LPA_3 receptor., *J. Biol. Chem.*, **278**, 11962-11969 (2003).

SB-239063: p38 MAP kinase inhibitor

Prod. No. **S 0569**



Numerous mediators believed to play a role in endothelial dysfunction (e.g., neurohormones, cytokines, hypoxia, and stress) have been shown to activate p38 mitogen-activated protein kinase (MAPK) in a variety of cell types [1,2]. **p38 MAPK** (Prod. No. **M 8057**) plays an important role in endothelial inflammation and dysfunction as well as p38 MAPK-dependent hypertension [1,2].

SB-239063 is a potent p38 MAPK inhibitor that has been shown to block purified p38 MAPK, displaying an IC_{50} value of 44 nM in **LPS** (Prod. No. **L 4391**)-stimulated human peripheral blood monocytes [1].

SB-239063 therefore provides researchers with an additional tool with which to study asthma, chronic airway diseases, inflammatory disorders, ischemic stroke, hypertension, renal dysfunction and diabetic neuropathy.

References

1. Underwood, D.C., et al., SB 239063, a potent p38 MAP kinase inhibitor, reduces inflammatory cytokine production, airways eosinophil infiltration, and persistence., *J. Pharmacol. Exp. Ther.*, **293**, 281-288 (2000).
2. Ju, H., et al., p38 MAPK inhibitors ameliorate target organ damage in hypertension: Part 1. p38 MAPK-dependent endothelial dysfunction and hypertension., *J. Pharmacol. Exp. Ther.*, **307**, 932-938 (2003).

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Anti-Tuberin (IA-22): Protein product of the tumor suppressor gene TSC2

Prod. No. **T 9574**

Developed in rabbit, affinity isolated antibody

Immunogen: synthetic peptide corresponding to human tuberin (amino acids 1463-1484); the corresponding sequence differs by two amino acids in rat and mouse

Species Reactivity: Human, mouse and rat

Tuberin is the protein product of the tumor suppressor gene TSC2 which contains two coiled-coil regions that mediate binding to hamartin, the protein product of the tumor suppressor gene TSC1 [1]. Tuberin and hamartin are involved in the regulation of cell cycle, cell growth, cell differentiation, cell adhesion and vesicular trafficking [2]. Mutations in either the TSC1 or the TSC2 gene are responsible for tuberous sclerosis complex (TSC), an autosomal dominant hereditary disease characterized by mental retardation, seizures and benign tumors (hamartomas) in multiple organs including the kidney, brain, heart and skin.

In immunoblotting studies, the antibody detects a band at 180-200 kDa using whole extracts of rat brain and mouse NIH-3T3 cells. In applications involving immunoprecipitation, the antibody immunoprecipitates tuberin from RIPA extract of human MCF-7 cells.

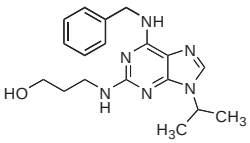
Anti-Hamartin (Prod. No. **H 2538**) is also available.

References

1. van Slegtenhorst, M., et al., Interaction between hamartin and turberin, the TSC1 and TSC2 gene products., *Hum. Mol. Genet.*, **7**, 1053-1057 (1998).
2. Dan, H.C., et al., Phosphatidylinositol 3-kinase/Akt pathway regulates tuberous sclerosis tumor suppressor complex by phosphorylation of tuberin., *J. Biol. Chem.*, **277**, 35364-35370 (2002).

Bohemine: Cyclin-dependent kinase (cdk) inhibitor

Prod. No. **B 0435**



Eight cyclin-dependent kinases, referred to as cdk-1 to cdk-8, together with their endogenous activator proteins called cyclins, form the autonomous oscillator that controls the cell cycle in embryonic, somatic and germline cells [1]. The activity of cdks is controlled through their dephosphorylation, subcellular localization and complex-formation with cyclins whose expression level is tightly regulated in keeping with the various phases of the cell cycle.

Bohemine, a synthetic purine analog, is a novel cell-permeable cdk inhibitor that possesses similar activity to **olomoucine** (Prod. No. **O 0886**) [2]. In *in vitro* assays using recombinant cdk1/cyclin B and cdk2/cyclin E kinase, IC_{50} values for bohemine were 1.1 µM [2] and 0.8 µM [3], respectively.

When examined for its ability to induce growth inhibition of various tumor cell lines, IC_{50} values of 28 µM, 113 µM, 27 µM, 58 µM and 45 µM were determined for MCF7, K562, CEM, HOS and G361 cell lines, respectively [3].

Bohemine represents an important addition to the growing arsenal of tools that will aid further understanding of the tightly orchestrated molecular associations and events that control the cell cycle.

References

1. Murray, A.W., Recycling the cell cycle: cyclins revisited., *Cell*, **116**, 221-234 (2004).
2. Krystof, V., et al., Synthesis and biological activity of olomoucine II., *Bioorg. Med. Chem. Lett.*, **12**, 3283-3286 (2002).
3. Otyepka, M, et al., Docking-based development of purine-like inhibitors of cyclin-dependent kinase-2., *J. Med. Chem.*, **43**, 2506-2513 (2000).