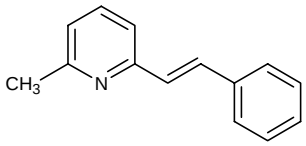
3050 Spruce Street
Saint Louis, Missouri 63103 USA
Telephone 800-325-5832 • (314) 771-5765
Fax (314) 286-7828
email: techserv@sial.com
sigma-aldrich.com

ProductInformation

SIB–1893

Product Number **S 9311**
Storage Temperature 2 to 8 °C

Cas #: 7370-21-0
Synonyms: (E)–2–Methyl–6–(2–phenylethenyl)pyridine



Product Description
Molecular Formula: $C_{14}H_{13}N$
Molecular Weight: 195.26 (anhydrous)
Appearance: yellow solid
Purity: >99% (HPLC)
Melting Point: 43.4-43.9 °C

Glutamate is the principal excitatory transmitter in the central nervous system acting through ionotropic glutamate receptors. It also plays a major role in activating modulatory pathways through the metabotropic glutamate receptors (mGluRs). mGluRs are G protein–coupled receptors and belong to the seven transmembrane spanning superfamily of receptors. The activation of mGluRs is involved in modulating synaptic transmission or neuronal signaling. To date, eight mGluRs have been cloned and functionally expressed. They are classified into three groups based on their amino acid sequence homology. Group I mGluRs includes mGluR1 and mGluR5 and is coupled to stimulation of phospholipase C, resulting in phosphoinositide hydrolysis and elevation of intracellular Ca^{2+} levels. Group I mGluRs also modulate ion channels, such as K^+ channels, Ca^{2+} channels, and nonselective cation channels. Group II (mGluR2 and mGluR3) and group III (mGluR4, mGluR6, mGluR7, and mGluR8) couple to inhibition of cAMP formation when heterologously expressed in mammalian cells. [1-33]

Group I receptors activate different pathways depending on their phosphorylation state. They can be activated either by extracellular signals, such as glutamate, or by intracellular proteins,[3,4] and are highly expressed in cortex, thalamus, hipoccampus and cerebellum. Postsynaptic activation of Group I receptors is thought to augment neurodegeneration mediated by the ion channel glutamate.[5]

Until recently very few Group I receptor-specific antagonists were available. SIB-1893 is new selective and noncompetitive antagonist of metabotropic glutamate receptor type 5 (GluR5). SIB-1893 inhibits the glutamate-induced Ca^{2+} response in hmGluR5a/L38-20 cells with an IC_{50} value of 0.29 µM, with minimal inhibition of hmGluR1b at concentrations up to 100 µM (i.e., >340-fold selectivity).[6] SIB-1893 inhibits the quisqualate-induced InsP accumulation in hmGluR5a/L38-20 cells with an IC_{50} value of 2.3 µM, with minimal inhibition at hmGluR1b/L13-23-7 cells at concentrations up to 100 µM.[6]

SIB-1893 inhibits (*S*)-3,5-dihydroxyphenylglycine (DHPG)-evoked inositol phosphate accumulation in hippocampus and striatum by 60% to 80%, with potency similar to that observed with recombinant mGluR5. SIB-1893, at 100 µM, did not show agonist activity at hmGluR2, hmGluR6, hmGluR7b, or hmGluR8a, but did exhibit some agonist activity at hmGluR4a at EC_{50} of 20.9 µg/ml. SIB-1893 showed no antagonist activities at group II or group III mGluRs in the cAMP or [^{35}S]GTPγS binding assays. Because this antagonist is noncompetitive, it offers additional advantage of being able to antagonize the receptor even in the presence of high levels of glutamate that occur in the diseased states. The excessive activation of mGluR5 has been implicated in many diseases, including epilepsy, cerebral ischemia, chronic neurodegeneration, pain, and psychiatric disorders. SIB-1893 will be important tools in determining the role of mGluR5 in animal models of these disorders. [5,6]

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Preparation Instructions
SIB-1893 is soluble in DMSO at 18 mg/ml. It is insoluble in water.

Storage/Stability
Store at 2 to 8 °C, tightly sealed, desiccated.

References

1. Pin, J. P., Duvoisin, R., The metabotropic glutamate receptors: structure and functions., Neuropharmacology., **34**, 1-26 (1995).
2. Brauner-Osborne, H., et al., Ligands for glutamate receptors: design and therapeutic prospects., J. Med. Chem., **43**, 2609-2645 (2000).
3. Kunishima, N., et al., Structural basis of glutamate recognition by a dimeric metabotropic glutamate receptor., Nature, **407**, 971-977 (2000).
4. Ango, F., et al., Agonist-independent activation of metabotropic glutamate receptors by the intracellular protein Homer., Nature, **411**, 962-965 (2001).
5. Francesconi, A., Opposing effects of protein kinase C and protein kinase A on metabotropic glutamate receptor signaling: selective desensitization of the inositol trisphosphate/Ca2+ pathway by phosphorylation of the receptor-G protein-coupling domain., Proc. Natl. Acad. Sci. U S A., **97**, 6185-6190 (2000).
6. Varney, M. A., et al., SIB-1757 and SIB-1893: selective, noncompetitive antagonists of metabotropic glutamate receptor type 5., J. Pharmacol. Exp. Ther., **290**, 170-181 (1999).

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