**Topiramate: Novel anticonvulsant and kainate GluR5 receptor antagonist**

Available First from Sigma-RBI

Prod. Code **T 0575**

Topiramate is a structurally novel anticonvulsant [1] that may also be efficacious in the treatment of chronic pain, obesity [2], post-traumatic stress disorder and migraine [3]. Topiramate appears to act as an antagonist at the GluR5 subtype of the kainate receptor [4,5] and displays an IC_{50} value of 0.5 µM in whole cell recording of the principal neurons of the rat basolateral amygdala [5].

**References**

5. Gwyer, D.S. and Jerman, J., The physiology and pharmacology of the orexins.

**SB-408124: Selective non-peptide OX₁ orexin receptor antagonist**

Prod. Code **S 2694**

Orexin-A and Orexin-B, also known as Hypocretin-1 and Hypocretin-2, are neuropeptides that have been isolated from the rat hypothalamus [1]. They have been implicated in the control of feeding, drinking, regulation of arousal and the sleep-wake cycle [1-4].

SB-408124 is a selective, non-peptide OX₁ orexin receptor antagonist that displays Kᵢ values of 27 nM and 99 nM in the membrane scintillation proximity assay (SPA) format and whole-cell assay, respectively [5]. This compound acts as a functional antagonist, as determined using a calcium mobilization assay and displays a Kᵢ value of 21.7 nM at the human OX₁ orexin receptor expressed in Chinese hamster ovary cells [5]. It also dose-dependently blocks orexin-A induced grooming following oral administration in rats [6].

SB-408124 will serve as a unique tool with which to elucidate the function of the OX₁ orexin receptor.

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**YIC-C8-434: Acyl-CoA: Cholesterol O-Acyltransferase (ACAT) inhibitor**

Prod. Code **Y 0628**

Acyl CoA cholesterol O-acyltransferase (ACAT, EC 2.3.1.26) is the enzyme responsible for the intracellular esterification of cholesterol. In the liver, ACAT-derived cholesteryl esters are secreted as a component of very low-density lipoprotein (VLDL). In the gastrointestinal tract, ACAT-mediated cholesterol esterification is the rate-limiting step in the absorption of food- and bile-derived cholesterol. YIC-C8-434, an ACAT inhibitor, inhibits the formation of cholesteryl esters and cholesterol both in human colon adenocarcinoma Caco2 cells and in human hepatoma HepG2 cells, displaying IC_{50} values of 0.38 and 0.49 µM, respectively [1]. Oral administration of YIC-C8-434 to rats at a dose of 8.3 mg/kg inhibited [14C] cholesterol absorption by 17% (p<0.01) and reduced intestinal cholesterol absorption and hepatic VLDL cholesterol secretion by direct inhibition of ACAT [1].

**References**


**GW311616A: Human neutrophil elastase (HNE) inhibitor**

Prod. Code **G 8419**

GW311616A is a potent, cell permeable, orally bioavailable and selective inhibitor of human neutrophil elastase (HNE) [1]. HNE is serine protease of the trypsin class. Normal lung maintains a balance between trypsin class enzymes and endogenous anti-trypsin (α1-protease inhibitor, α1-PI). In smokers’ lungs, the recruitment of inflammatory leukocytes such as neutrophils with the release of HNE and the inactivation of α1-PI by tobacco products lead to the disruption of this protective mechanism and pathologic destruction of the lung extracellular matrix. Small molecule HNE inhibitors are part of a general anti-protease strategy used in treatments for emphysema and COPD (Chronic Obstructive Pulmonary Disease) [2].

The Kᵢ value of GW311616A for purified HNE is 0.31 nM [3]. In contrast, its IC_{50} values for chymotrypsin (Prod. No. C 6423), trypsin and cathepsin G are 4.2 µM, >100 µM and >100 µM, respectively [3]. In addition, GW311616A inhibited HNE in human whole blood, possessing an IC_{50} value of 0.67 mM, in addition to inhibiting HNE in vivo in hamster and canine following oral administration [3].

**References**