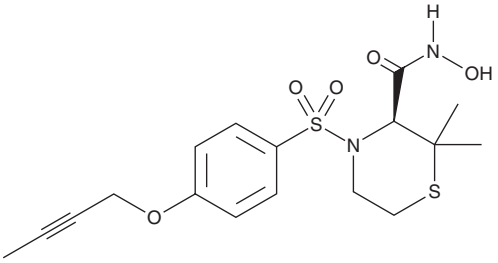
PRODUCT INFORMATION

TMI 1

Item No. 29713

CAS Registry No.: 287403-39-8
Formal Name: (3S)-4-[[4-(2-butyn-1-yloxy)phenyl] sulfonyl]-N-hydroxy-2,2-dimethyl-3-thiomorpholinecarboxamide
MF: $C_{17}H_{22}N_2O_5S_2$
FW: 398.5
Purity: ≥98%
Supplied as: A solid
Storage: -20°C
Stability: ≥4 years



Information represents the product specifications. Batch specific analytical results are provided on each certificate of analysis.

Laboratory Procedures

TMI 1 is supplied as a solid. A stock solution may be made by dissolving the TMI 1 in the solvent of choice, which should be purged with an inert gas. TMI 1 is soluble in the organic solvent DMSO at a concentration of approximately 25 mg/ml.

Description

TMI 1 is an inhibitor of disintegrin and metalloproteinase domain-containing protein 17 (ADAM17/TACE; IC_{50} = 8.4 nM in a cell-free enzyme assay).[1] It inhibits matrix metalloproteinase-1 (MMP-1), -2, -7, -9, -13, and -14, as well as ADAM-TS-4 *in vitro* (IC_{50}s = 6.6, 4.7, 26, 12, 3, 26, and 100 nM, respectively). It also inhibits ADAM8, -10, -12, and -17/TACE in cell-free enzyme assays with K_i values of 21, 16, 1.8, and 0.079 nM, respectively, with slow-binding inhibition of ADAM17/TACE but not the other ADAM enzymes.[2] TMI 1 inhibits LPS-induced TNF-α secretion in Raw and THP-1 cells (IC_{50}s = 40 and 200 nM, respectively), as well as in isolated human monocytes and whole blood (IC_{50}s = 190 and 300 nM, respectively).[1] It inhibits the production of TNF-α *ex vivo* in synovium isolated from the inflamed joints of patients with rheumatoid arthritis with IC_{50} values of less than 100 nM without inhibiting TNF-α expression *in vitro*. TMI 1 inhibits LPS-induced TNF-α production in mice (ED_{50} = 5 mg/kg) and reduces disease severity in mouse models of collagen-induced arthritis. It also decreases cell viability of (ED_{50}s = 1.3-8.1 µM), and induces caspase-3/7 activity in, a variety of cancer cell lines and induces tumor apoptosis and reduces tumor growth in an MMTV-ErbB2/neu mouse model of breast cancer when administered at a dose of 100 mg/kg.[3]

References

1. Zhang, Y., Xu, J., Levin, J., *et al.* Identification and characterization of 4-[[4-(2-butynyloxy)phenyl] sulfonyl]-N-hydroxy-2,2-dimethyl-(3S)thiomorpholinecarboxamide (TMI-1), a novel dual tumor necrosis factor-α-converting enzyme/matrix metalloprotease inhibitor for the treatment of rheumatoid arthritis. *J. Pharmacol. Exp. Ther.* **309(1),** 348-355 (2004).
2. Moss, M.L. and Rasmussen, F.H. Fluorescent substrates for the proteinases ADAM17, ADAM10, ADAM8, and ADAM12 useful for high-throughput inhibitor screening. *Anal. Biochem.* **366(2),** 144-148 (2007).
3. Mezil, L., Berruyer-Pouyet, C., Cabaud, O., *et al.* Tumor selective cytotoxic action of a thiomorpholin hydroxamate inhibitor (TMI-1) in breast cancer. *PLoS One* **7(9),** e43409 (2012).

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