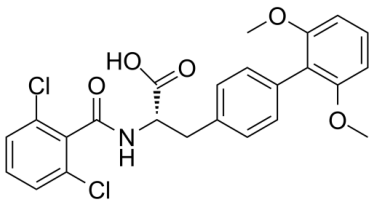
Data Sheet

Product Name:	TR-14035
Cat. No.:	CS-1812
CAS No.:	232271-19-1
Molecular Formula:	C24H21Cl2NO5
Molecular Weight:	474.33
Target:	Integrin
Pathway:	Cytoskeleton
Solubility:	DMSO : ≥ 41 mg/mL (86.44 mM)



BIOLOGICAL ACTIVITY:

TR-14035 is a a dual alpha4beta7(IC50=7 nM)/alpha4beta1 (IC50=87 nM) integrin antagonist . IC50 Value: alpha(4)beta(7)/alpha(4)beta(1)=7/87 nM [1] Target: integrin TR14035 blocked the binding of human alpha(4)beta(7) to an (125)I-MAdCAM-Ig fusion protein with IC(50) values of 0.75 nM. TR14035 blocked binding of human alpha(4)beta(7)-expressing RPMI-8866 cells or murine mesenteric lymph node lymphocytes to MAdCAM-Ig with IC(50) values of 0.1 microM [2]. TR14035 blocked adhesion to HEVs [ED(50) of 0.01-0.1 mpk i.v.]. TR-14035 was taken up by rat and human hepatocytes by an apparently single saturable mechanism with K(m) of 6.7 and 2.1 microM, respectively, and taurocholate and digoxin reduced this uptake [3].

PROTOCOL (Extracted from published papers and Only for reference)

Cell assay [2] An in vitro shear flow system adapted from published methods (Berlin et al., 1993) was used to evaluate the ability of TR-14035 to block the binding of human RPMI-8866 cells or murine MLN lymphocytes (2 × 106 cells/ml) isolated from BALB/c mice to capillary tubes coated with murine or human MAdCAM-Ig, respectively. Cells at a density of 6 × 106cells/ml were preincubated with TR-14035 (0.06–6 μM; final DMSO <1%), neutralizing mAb, or isotype control mAb at 0.6 μM in buffer (HBSS without Ca2+/Mg2+, 20 mM HEPES, 2 mM Mn2+, and 2% human serum, pH 7.0) for 10 min at 37°C. A 500-μl cell suspension was then injected into a closed loop flow system that contained 2.5 ml of assay buffer (HBSS with Ca2+/Mg2+, 20 mM HEPES, and 2% human serum, pH 7.0). Murine assays included preincubation of cells with anti-L-selectin at 0.6 μM to blockL-selectin-dependent rolling due to interactions with the mucin domain of mMAdCAM-Ig. A silicone tubing loop and roller pump were used to circulate cells through a MAdCAM-Ig-coated capillary tube mounted on an inverted microscope stage. MAdCAM-Ig was titrated (5, 10, and 50 μg/ml), and 50 μg/ml was selected for use because it supported 50 to 150 interacting cells/field after 15 min of continuous shear flow. The shear rate was 2 dynes/cm2 for the first 5 min and 1.2 dynes/cm2 for the last 10 min, simulating physiological shear flow, where noninteracting lymphocytes have a midline velocity of 4000 μm/s in murine HEVs (Bargatze et al., 1995). Cells were monitored for 15 min by videomicroscopy, and the number of adherent cells was determined at 1-min intervals by analysis of individual frames using either a customized Proteo-Flow computer analysis package (LigoCyte Pharmaceuticals) or manual counting directly from the monitor screen. Control adhesion for individual experiments was based on the isotype or 1% DMSO control treatment. Data are represented as area under the curve (AUC) from time 0 to 15 min. Data were normalized by calculating percentage of control adhesion within each experiment, with two to six tests evaluated per treatment.

References:

[1]. Sircar I, et al. Synthesis and SAR of N-benzoyl-L-biphenylalanine derivatives: discovery of TR-14035, a dual alpha(4)beta(7)/alpha(4)beta(1) integrin antagonist. Bioorg Med Chem. 2002 Jun;10(6):2051-66.

[2]. Egger LA, et al. Alpha(4)beta(7)/alpha(4)beta(1) dual integrin antagonists block alpha(4)beta(7)-dependent adhesion under shear flow. J Pharmacol Exp Ther. 2002 Jul;302(1):153-62.

CAIndexNames:

[1,1'-Biphenyl]-4-propanoic acid, α-[(2,6-dichlorobenzoyl)amino]-2',6'-dimethoxy-,(αS)-

SMILES:

COC1=C(C2=CC=C(C[C@@H](C(O)=O)NC(C3=C(Cl)C=CC=C3Cl)=O)C=C2)C(OC)=CC=C1

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