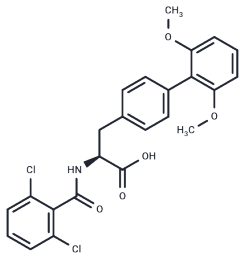
Data Sheet (Cat.No.T5310)

TargetMol

TR-14035

Chemical Properties



CAS No. : 232271-19-1

Formula: C24H21Cl2NO5

Molecular Weight: 474.33

Storage: Powder: -20°C for 3 years | In solvent: -80°C for 1 year
Actual storage temperature shall be subject to the COA.

Biological Description

Description	TR-14035 (MDK-1191) is a dual antagonist of α4β7/α4β1 integrins (IC50s: 7/87nM).
Targets(IC50)	Integrin
In vitro	TR-14035 (IC50: alpha(4)beta(7)/alpha(4)beta(1)=7/87 nM) has completed Phase I studies in Europe [1]. 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. OATP1B1/OATP-C and OATP1B3/OATP8 expressed in oocytes mediated the TR-14035 uptake with K(m) of 7.5 and 5.3 microM, respectively [2]. TR14035 blocked the binding of human alpha(4)beta(7) to a (125)I-MAdCAM-Ig fusion protein with IC(50) values of 0.75 nM. Under shear flow in vitro, 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 [3].
In vivo	Biliary excretion and total body clearance of unchanged TR-14035 in EHBRs were significantly lower than those in normal rats, while there was no difference in the clearances between wild and mdr1a/b- or Bcrp-knockout mice [2]. TR14035 blocked adhesion to HEVs (ED50: of 0.01-0.1 mpk i.v.) [3].
Cell Research	RPMI8866 cell line and Jurkat T lymphoblastoid cell line were grown as a suspension culture in RPMI 1640 media, 10% FCS, 2 mM glutamine, 100 units/mL penicillin G, 100 mg/mL streptomycin sulfate at 37 °C and 5% CO2. Adhesion assays have been detailed elsewhere. Microtiter plates were coated with 20 mg/mL HSA for 2 h at room temperature, washed once with PBS and derivatized with 10 mg/mL SPDP for 1 h. After washing, CS-1 (or sCS-1) derived peptide solution (100 mL at 100 μg/mL) was added to the wells and allowed to crosslink to the plates overnight at 4 °C. Non-reacted sites were blocked with 100 mL of 1% OV in PBS for 1 h at 37 °C. RPMI8866 cells were suspended in Dulbecco's modified Eagle's medium with 0.25% OV at a density of 2.5 ×106/mL and incubated for ~1 h at 37 °C with varying concentrations of antagonists on peptide-coated plates. Following washing (EL404 plate washer), bound cells were quantified by measuring endogenous N-acetyl-hexosaminidase activity by reading the optical density at 405 nm using the enzyme substrate p-nitrophenol-N-acetyl-b-d-glucoseaminide. IC50 values were generated by nonlinear regression from titration curves of antagonists from seven doses and reported as the average of a minimum of two experiments. Since

Cell Research	experimental variability was noted with respect to the IC50 of the internal standard [(1S - cis) - N - [(3 - carboxy - 2,2,3 - trimethylcyclopentyl)- carbonyl]-O-[(2,6-dichlorophenyl) methyl]-l-tyrosine] a normalization procedure was done using the global mean value [IC50=0.224±0.17 μM (N=19)] of the internal standard. For the Jurkat cell adhesion assay, OV was replaced with 0.25% HSA for both blocking and adhesion buffers. Standard error of the mean for the Jurkat cell adhesion assay was typically <10% for each experiment and no normalization was needed [1].
Animal Research	For biliary excretion studies in mice and rats, a cannula (polyethylene tube, SP8 for mice and SP10 for rats) was inserted into the bile duct of the anesthetized animal. In the rat, after complete recovery from diethyl ether anesthesia, TR-14035 was administered intravenously at a dose of 3 mg/ml/kg, and the bile, urine, and blood were collected at designated time intervals. In the mouse, TR-14035 was administered intravenously at a dose of 3 mg/4 ml/kg, and the bile and blood were collected at designated time intervals under pentobarbital anesthesia. Blood was centrifuged to separate plasma, and all the samples were stored at j20 -C until analysis by LC-MSD [2].

Solubility Information

Solubility	H2O: Insoluble, DMSO: 40 mg/mL (84.33 mM),Sonication is recommended. (< 1 mg/ml refers to the product slightly soluble or insoluble)
In vivo Formulation	10% DMSO+40% PEG300+5% Tween 80+45% Saline: 2 mg/mL (4.22 mM),Sonication is recommended. *Please add the solvents sequentially, clarifying the solution as much as possible before adding the next one. Dissolve by heating and/or sonication if necessary. Working solution is recommended to be prepared and used immediately. The formulation provided above is for reference purposes only. In vivo formulations may vary and should be modified based on specific experimental conditions.*

Preparing Stock Solutions

	1mg	5mg	10mg
1 mM	2.1082 mL	10.5412 mL	21.0824 mL
5 mM	0.4216 mL	2.1082 mL	4.2165 mL
10 mM	0.2108 mL	1.0541 mL	2.1082 mL
50 mM	0.0422 mL	0.2108 mL	0.4216 mL

Please select the appropriate solvent to prepare the stock solution, according to the solubility of the product in different solvents. Please use it as soon as possible.

Note: The dilution table applies only to solid products. For liquid products, please calculate the stock solution based on the stated concentration and/or density.

Reference

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.
Tsuda-Tsukimoto M, et al. Characterization of hepatobiliary transport systems of a novel alpha4beta1/alpha4beta7 dual antagonist, TR-14035. Pharm Res. 2006 Nov;23(11):2646-56.
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.

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