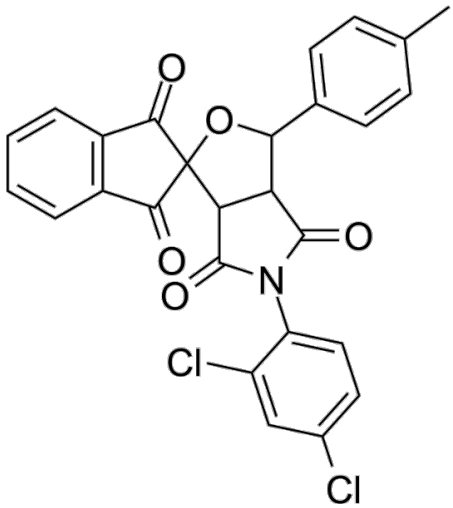
Product Data Sheet

Product Name: ML-T7
Cat. No.: GC26676

Chemical Properties

Cas. No.	459789-75-4		
SMILES	O=C1C2=C(C(C13OC(C4C(N(C5=CC=C(C=C5Cl)Cl)C(C43)=O)=O)C6=CC=C(C)C=C6)=O)C=CC=C2		
Formula	$C_{27}H_{17}Cl_2NO_5$	M.Wt	506.33
Solubility	DMSO : 66.67 mg/mL (131.67 mM; Need ultrasonic)	Storage	-20°C
General tips	For obtaining a higher solubility , please warm the tube at 37 °C and shake it in the ultrasonic bath for a while.Stock solution can be stored below -20°C for several months.		
Shipping Condition	Evaluation sample solution : ship with blue ice All other available size: ship with RT , or blue ice upon request.		

Structure



Protocol

Cell experiment [1]:

Cell lines Bone marrow cells

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Preparation Method	For generation of dendritic cells (DCs), bone marrow cells were isolated by flushing femurs, tibias and humeri and plated in RPMI1640 medium supplemented with 10% FBS, 1% penicillin-streptomycin, 50μM 2-Mercaptoethanol, 10ng/mL GM-CSF and 5ng/ml IL-4. After 6 days, 10μg/mL LPS was used to induce DC maturation in the presence of DMSO or ML-T7. DC maturation markers were detected using flow cytometric analysis 24h later.
Reaction Conditions	10μM; 24h
Applications	ML-T7 enhanced maturation marker expression and antigen-presenting capacity in LPS (1μg/mL)-stimulated DC.

Animal experiment [2]:

Animal models	Akt/cMyc–induced HCC C57BL/6 mice models
Preparation Method	Mice were treated with ML-T7 at different doses (DMSO as control, every 2 days) from day 13 to day 32.
Dosage form	20 and 50mg/kg; i.p.; every 2 days for 20days

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Applications	Mouse body weight showed no significant difference during treatment with ML-T7 at different doses. Compared with control treatment with DMSO, treatment with ML-T7 at doses of 20 and 50mg/kg markedly inhibited tumor growth as measured by in vivo bioluminescence imaging and prolonged survival. Liver-to-body weight ratios, as well as serum concentrations of aspartate aminotransferase (AST) and alanine aminotransferase (ALT), were suppressed by ML-T7 at doses of 20 and 50mg/kg. Systemic administration of ML-T7 at doses of 20 and 50mg/kg caused significantly increased $CD8^+$ T cells and increased the Ki67-positive $CD8^+$ T cells in both tumor and spleen. ML-T7 enhanced the polyfunctionality (coproduction of IFN-γ, TNF-α, and IL-2) of tumor-infiltrating and splenic $CD8^+$ T cells and reduced the expression of PD-1 in $CD8^+$ T cells, implying an inhibition of T cell exhaustion.

References:

[1] Ma, Shuaiya et al. “Identification of a small-molecule Tim-3 inhibitor to potentiate T cell-mediated antitumor immunotherapy in preclinical mouse models.” Science translational medicine vol. 15,722 (2023): eadg6752.

Background

ML-T7 is a potent T cell immunoglobulin and mucin domain-containing protein 3 (Tim-3) inhibitor, which targets the FG-CC’ loop and binds to Tim-3 to disrupt the interaction between Tim-3 and phosphatidylserine/carcinoembryonic antigen–related cell adhesion molecule 1 (PtdSer/CEACAM1). The Kd values of ML-T7 binds to hTim-3 and mTim-3 are 6.98 and 7.40μM, respectively. Tim-3 is highly expressed on exhausted T cells in tumors and mediates T-cell terminal differentiation and exhaustion during chronic viral infection and tumor progression. ML-T7 promoted T cell survival and suppressed T cell exhaustion to enhance the antitumor activity of $CD8^+$ cytotoxic T lymphocytes (CTLs) and chimeric antigen receptor (CAR) T cells in vitro and in vivo[1].

In vitro, ML-T7 (1-20μM; 4h) dose-dependently promoted cell proliferation, cytokine production, and cytotoxicity of C57BL/6-Tg(TcraTcrb)1100Mjb/J (OT-I) mice $CD8^+$ CTLs[1]. ML-T7 (10μM; 48h) significantly enhanced the production of IFN-γ, TNF-α, CD107a, and granzyme B in the human NK92

and increased its cytotoxic activity against K562-Fluc cells at different effector-to-target (E:T) ratios[1]. ML-T7 (10μM; 24h) enhanced maturation marker expression and antigen-presenting capacity in LPS (1μg/mL)-stimulated dendritic cells (DC)[1].

In vivo, ML-T7 (20 and 50mg/kg; i.p.; every 2 days for 20 days) enhanced dendritic cell maturation, increased the infiltration and multifunctionality of $CD8^+$ T cells, and reduced PD-1 expression and T-cell exhaustion, thereby significantly inhibiting tumor growth and prolonging survival in Akt/c-Myc-induced HCC C57BL/6 mice models[1]. ML-T7 (50mg/kg; i.p.; every 2 days for 20 days) increased the number and activity of $CD8^+$ T cells in tumors and spleens, alleviated T-cell exhaustion, enhanced NK-cell function and dendritic cell maturation, and significantly suppressed tumor progression and prolonged survival in Akt/N-Ras-induced HCC mouse model[1].

References:
[1] Ma, Shuaiya et al. “Identification of a small-molecule Tim-3 inhibitor to potentiate T cell-mediated antitumor immunotherapy in preclinical mouse models.” Science translational medicine vol. 15,722 (2023): eadg6752.