# ITK degrader 1

**Cat. No.:** HY-149917

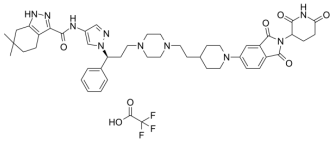
**Molecular Formula:** $C_{48}H_{57}F_3N_{10}O_7$

**Molecular Weight:** 943.02

**Target:** Itk

**Pathway:** Protein Tyrosine Kinase/RTK

**Storage:** Please store the product under the recommended conditions in the Certificate of Analysis.



## BIOLOGICAL ACTIVITY

**Description**

ITK degrader 1 is a highly selective degrader of interleukin-2-inducible T-cell kinase (ITK; $DC_{50}$=3.6 nM in vivo in mice). ITK degrader 1 induces rapid, and prolonged ITK degradation and suppresses IL-2 secretion ($EC_{50}$=35.2 nM, Jurkat cells) stimulated by anti-CD3 antibodyin vivo. ITK degrader 1 also shows good plasma exposure levels[1].

**In Vitro**

ITK degrader 1 (compound 28) (0.001-3 μM; 12 h) dose-dependently decreases the protein levels of ITK in Jurkat cells[1].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Western Blot Analysis[1]

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| Cell Line: | Jurkat cells |
| Concentration: | 0.001 μM, 0.003 μM, 0.1 μM, 0.3 μM, 1 μM, 3 μM |
| Incubation Time: | 12 h |
| Result: | Exhibited strong ITK degradation potencies in a dose-dependent manner. Even rapidly led to significant ITK protein downregulation after 1 h incubation. |

**In Vivo**

ITK degrader 1 (compound 28) (20 mg/kg; ip; single dose) significantly degrades ITK protein 2 h, 8 h, and 16 h after treatment on mice. ITK degrader 1 (25 mg/kg; ip; single dose) also inhibits inhibits IL-2 secretion 6 h after treatment in vivo in anti-CD3 monoclonal antibody (mAb)-induced IL-2 mouse model[1].

Pharmacokinetic Analysis in Balb/c Mice[1]

| Route | Dose (mg/kg) | $AUC_{0-t}$ (ng·h/mL) | $AUC_{0-\infty}$ (ng·h/mL) | $T_{1/2}$ (h) | $V_z$ (L/kg) | Cl (mL/min/kg) | $C_{max}$ (ng/mL) | $MRT_{last}$ (h) | Bioavailability (%) |
|---|---|---|---|---|---|---|---|---|---|
| i.v. | 5 | 15138 | 15415 | 4.39 | 2057 | 5.4 | 4910 | 4.42 | / |
| ip | 10 | 25931 | 27261 | 5.75 | 3055 | 6.1 | 3423 | 5.84 | 88.4% |

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|---|---|
| Animal Model: | Balb/c mice, and anti-CD3 mAb-induced IL-2 mouse model[1] |
| Dosage: | 20 mg/kg, 25 mg/kg |
| Administration: | IP; singel dose |
| Result: | Successfully delivered to the peripheral blood and spleen tissue, eliciting efficient, rapid, and prolonged ITK degradation starting at 2 h and lasting for at least 16 h with 20 mg/kg dose in Balb/c mice.<br>Efficiently suppressed the production of cytokine IL-2, resulting in a reduction of over 70% compared to the vehicle group with 25 mg/kg dose. |

## REFERENCES

[1]. Zhou D, et al. Discovery of Potent and Highly Selective Interleukin-2-Inducible T-Cell Kinase Degraders with In Vivo Activity. J Med Chem. 2023 Apr 13;66(7):4979-4998.



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