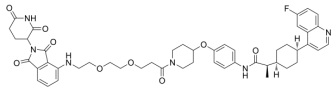
NU223612

Cat. No.:	HY-151886
CAS No.:	2759420-43-2
Molecular Formula:	$C_{49}H_{55}FN_6O_9$
Molecular Weight:	890.99
Target:	PROTACs; Indoleamine 2,3-Dioxygenase (IDO)
Pathway:	PROTAC; Metabolic Enzyme/Protease
Storage:	Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description

NU223612 is a potent PROTAC (PROTACs) that degrades indoleamine 2,3-dioxygenase 1 (IDO1) (Indoleamine 2,3-Dioxygenase (IDO)) with a K_d of 640 nM. NU223612 potently degrades the IDO1 protein through CRBN-mediated proteasomal degradation. NU223612 is bound to CRBN with an affinity of 290 nM. NU223612 can cross the blood-brain barrier (BBB)[1].

IC_{50} & Target	Cereblon	IDO1 640 nM (Kd)

In Vitro

NU223612 (0.1-10 μM; 24 h) decreases IDO1 protein levels dose-dependently[1].
A DC_{50} (the concentration of the NU223612 at which 50% of the IDO1 protein is degraded) of 0.3290 μM and 0.5438 μM in U87 and GBM43 cells is determined, respectively[1].
NU223612 degrades IDO1 protein in multiple cell types, such as CD18 and PANC-1 human pancreatic cancer cells, OVCAR5 and SKOV3 human ovarian cancer cells, PC3 human prostate cancer cells, and the syngeneic GL261 mouse IDO1 cDNA-expressing (IDO1-O/E) glioma cell line[1].
NU223612 equally degrades IDO1 protein levels in both the cytoplasmic and nuclear intracellular compartments in human GBM cells. NU223612 is able to penetrate subcellular compartments[1].
NU223612 dose-dependently inhibits IDO1 enzyme activity resulting in decreased Kyn levels in cultured IFNγ-stimulated GBM cells. NU223612 inhibits both IDO1-mediated tryptophan metabolism as well as IDO1 non-enzyme-mediated NF-κB p65 transcription factor DNA binding activity[1].

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

Western Blot Analysis[1]

Cell Line:	U87 and human GBM43 cells
Concentration:	0 μM, 0.1 μM, 1 μM, and 10 μM
Incubation Time:	24 h
Result:	Decreased IDO1 protein levels dose-dependently.

In Vivo

NU223612 (25 mg/kg; i.p.; once) decreases IDO1 protein in C57BL/6 with mIDO1 cDNA-expressing GL261 cells[1].
NU223612 (25 mg/kg; i.p.; 5 days/week; for 3 weeks) leads to an increase in median overall survival as well as longer-term survival for up to 45 days post-tumor cell injection[1].
Mass spectrometry analysis of NU223612 (25 mg/kg; i.p.; once) shows a C_{max} of 2 μM and a half-life of 8.3 h in brain tissue. In

plasma, C_{max} is 365 μM and the half-life is 2.5 h. The binding of NU223612 to mouse brain homogenate using a 6 h equilibrium dialysis shows NU223612 to be 99.8% bound[1].
Half-life, AUC, and C_{max} of NU223612 in serum and brain samples[1].

	Plasma	Brain
half-lifr (h)	2.5	8.3
AUC_{0-24} (μM*h)	582	7
C_{max} (μM)	365	2

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

Animal Model:	Male C57BL/6 mice bearing GL261 cells[1]
Dosage:	25 mg/kg
Administration:	i.p.; once
Result:	Decreased IDO1 protein by >70% within 2 h post-treatment and remains low for up to 24 h.

Animal Model:	8 week old C57BL/6 wild-type (WT) mice are intracranially engrafted with luciferase-modified GL261 cells (GL261-luc.)[1]
Dosage:	25 mg/kg
Administration:	i.p.; 5 days/week; for 3 weeks
Result:	Led to an increase in median overall survival as well as longer-term survival for up to 45 days post-tumor cell injection.

REFERENCES

[1]. Lakshmi R Bollu, et al. Identification and Characterization of a Novel Indoleamine 2,3-Dioxygenase 1 Protein Degrader for Glioblastoma. J Med Chem. 2022 Nov 21.

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