Navoximod

Cat. No.: HY-18770B

CAS No.: 1402837-78-8

Molecular Formula: $C_{18}H_{21}FN_2O_2$

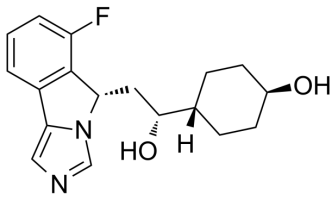
Molecular Weight: 316.37

Target: Indoleamine 2,3-Dioxygenase (IDO)

Pathway: Metabolic Enzyme/Protease

Storage: -20°C, stored under nitrogen

* In solvent : -80°C, 6 months; -20°C, 1 month (stored under nitrogen)



SOLVENT & SOLUBILITY

In Vitro

DMSO : 100 mg/mL (316.09 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	3.1609 mL	15.8043 mL	31.6086 mL
	5 mM	0.6322 mL	3.1609 mL	6.3217 mL
	10 mM	0.3161 mL	1.5804 mL	3.1609 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 3 mg/mL (9.48 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 3 mg/mL (9.48 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 3 mg/mL (9.48 mM); Clear solution
4. Add each solvent one by one: 5% DMSO >> 40% PEG300 >> 5% Tween-80 >> 50% saline
   Solubility: ≥ 2.5 mg/mL (7.90 mM); Clear solution
5. Add each solvent one by one: 5% DMSO >> 95% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (7.90 mM); Clear solution
6. Add each solvent one by one: 1% DMSO >> 99% saline
   Solubility: ≥ 0.5 mg/mL (1.58 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Navoximod (GDC-0919; NLG-919) is a potent IDO (indoleamine-(2,3)-dioxygenase) pathway inhibitor with K_i/EC_{50} of 7 nM/75 nM.

IC_{50} & Target	IDO 7 nM (Ki)	IDO 75 nM (EC50)

In Vitro

Using IDO-expressing human monocyte-derived dendritic cells (DCs) in allogeneic mixed lymphocyte reaction (MLR) reactions, Navoximod (NLG919) potently blocks IDO-induced T cell suppression and restores robust T cell responses with an ED_{50}=80 nM. Similarly, using IDO-expressing mouse DCs from tumor-draining lymph nodes, Navoximod abrogates IDO-induced suppression of antigen-specific T cells (OT-I) in vitro, with ED_{50}=120 nM[1]. Navoximod inhibits the IDO activity in a concentration-dependent manner with an EC_{50} of 0.95 μM. PEG2k-Fmoc-NLG(L) is less active (EC_{50} of 3.4 μM) in inhibiting IDO compared with free Navoximod while PEG2k-Fmoc-NLG(S) is least active (EC_{50}>10 μM). Coculture of IDO+tumor cells with splenocytes isolated from BALB/c mice leads to significant inhibition of T-cell proliferation. This inhibition is significantly attenuated when the mixed cells are treated with Navoximod. PEG2k-Fmoc-NLG(L) is also active in reversing the inhibitory effect of tumour cells although slightly less potent than Navoximod [3].

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

In Vivo

VNavoximod (NLG919) is orally bioavailable (F>70%); and has a favorable pharmacokinetic and toxicity profile. In mice, a single oral administration of Navoximod reduces the concentration of plasma and tissue Kyn by ~50%. In vivo, in mice bearing large established B16F10 tumors, administration of Navoximod markedly enhances the anti-tumor responses of naïve, resting pmel-1 cells to vaccination with cognate hgp100 peptide plus CpG-1826 in IFA. In this stringent established-tumor model, Navoximod plus pmel-1/vaccine produce a dramatic collapse of tumor size within 4 days of vaccination (~95% reduction in tumor volume compare to control animals receiving pmel-1/vaccine alone without Navoximod)[1]. When combined with NSC 362856 (TMZ)+radiation therapy (RT), both Navoximod and D-1MT (Indoximod) enhance survival relative to mice treated with TMZ+RT alone[2].

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PROTOCOL

Cell Assay [3]

The IDO inhibitory effect of PEG2k-Fmoc-NLG is tested by an in vitro IDO assay. Briefly, HeLa cells are seeded in a 96-well plate at a cell density of 5000 cells per well and allowed to grow overnight. Recombinant human IFN-γ is then added to each well with a final concentration of 50 ng/mL. At the same time, various concentrations of PEG2k-Fmoc-NLG(L), PEG2k-Fmoc-NLG(S) or Navoximod (NLG919) (50 nM-20 μM) are added to the cells. After 48 h of incubation, 150 μL of the supernatants per well is transferred to a new 96-well plate. Seventy-five μL of 30% trichloroacetic acid is added into each well and the mixture is incubated at 50°C for 30 min to hydrolyse N-formylkynurenine to kynurenine. For colorimetric assay, supernatants are transferred to a new 96-well plate, mixed with equal volume of Ehrlich reagent (2% p-dimethylamino-benzaldehyde w/v in glacial acetic acid), and incubated for 10 min at RT. Reaction product is measured at 490 nm by a plate reader[3].

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Animal Administration [2]

Mice[2]

Mice are immobilized in a stereotactic frame for tumor implantation. Briefly, the skull is shaved and exposed with a 0.5 cm skin incision. With antiseptic technique, 10^5 GL261 cells (suspended in 3 μL RPMI-1640) are injected at the following coordinates with respect to the bregma on the right side (antero-posterior, -2 mm; medio-lateral, 2 mm; dorso-ventral, 3 mm). This placement reproducibly yielded tumor growth in a paracortical area of the posterolateral right frontal lobe. Tumor-bearing mice are treated with combinations of oral DL-1MT (2 mg/mL D-1MT mixed with 2 mg/mL L-1MT) in drinking water, D-1MT (4 mg/mL) in drinking water, Navoximod (6 mg/mL) in drinking water, intraperitoneal NSC-26271, intraperitoneal NSC 362856, and/or total-body radiation (500 cGy from a ^{137}Cs source), as detailed in figure legends. Mice are observed daily, and sacrificed when they became ill or moribund[2].

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CUSTOMER VALIDATION

- Nano Today. October 2022, 101600.
- Nat Commun. 2022 Jul 12;13(1):4032.
- Chem Eng J. 478, 15 December 2023, 147465
- Adv Sci (Weinh). 2023 Oct 23:e2305150.
- Adv Sci (Weinh). 2019 Apr 18;6(12):1900327.

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REFERENCES

[1]. Mario R. Mautino, et al. Abstract 491: NLG919, a novel indoleamine-2,3-dioxygenase (IDO)-pathway inhibitor drug candidate for cancer therapy. AACR 104th Annual Meeting 2013; Apr 6-10, 2013.

[2]. Li M, et al. The indoleamine 2,3-dioxygenase pathway controls complement-dependent enhancement of chemo-radiation therapy against murine glioblastoma. J Immunother Cancer. 2014 Jul 7;2:21.

[3]. Chen Y, et al. An immunostimulatory dual-functional nanocarrier that improves cancer immunochemotherapy. Nat Commun. 2016 Nov 7;7:13443.

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