Product Data Sheet

Product Name: M3814 (nedisertib)
Cat. No.: GC32718

Chemical Properties

Cas. No.	1637542-33-6		
SMILES	COC1=CC=C([C@@H](O)C2=CC(C3=C(C=CC(N4CCOCC4)=C5)C5=NC=N3)=C(F)C=C2Cl)N=N1		
Formula	$C_{24}H_{21}ClFN_5O_3$	M.Wt	481.91
Solubility	DMSO : 100 mg/mL (207.51 mM);Water : < 0.1 mg/mL (insoluble)	Storage	Store at -20°C
General tips	For obtaining a higher solubility , please warm the tube at 37 ℃ and shake it in the ultrasonic bath for a while.Stock solution can be stored below -20℃ 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	M3814 (nedisertib)		

Protocol

Cell experiment [1]:

Cell lines	NCI-H460, NCI-H460/MX20, A549, A549/MX10, HEK293/pcDNA3.1, HEK293/ABCG2, KB-3-1, and KB-C2 cells

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Preparation Method	Cells were maintained in Dulbecco's minimal essential medium (DMEM) supplemented with 10% fetal bovine serum (FBS) and 1% penicillin/streptomycin at 37°C, 5% CO_2. For reversal studies, ABCG2-overexpressing resistant cells (NCI-H460/MX20, A549/MX10) and transfected cells (HEK293/ABCG2) were treated with M3814 at non-toxic concentrations (0.3-1μM) for 2 hours prior to and during exposure to ABCG2 substrate drugs (mitoxantrone, doxorubicin).
Reaction Conditions	0.3-1μM; 2-hour pretreatment followed by co-incubation with chemotherapeutic agents for 72 hours.
Applications	M3814 significantly reversed ABCG2-mediated multidrug resistance (MDR) by increasing the intracellular accumulation of substrate drugs in resistant cells. M3814 stimulated ABCG2 ATPase activity in a concentration-dependent manner

Animal experiment [2]:

Animal models	BALB/c mice with CT26 colorectal cancer subcutaneous xenografts
Preparation Method	Mice were implanted with 1×10^6 CT26 cells subcutaneously in the flank. When tumor volume reached 100mm^3, mice were randomized into treatment groups: vehicle, standard of care (SOC; 100mg/kg capecitabine with 2Gy radiation), 50mg/kg M3814 with 2Gy radiation, and SOC plus 50mg/kg M3814. Capecitabine and/or M3814 were administered via oral gavage on radiation treatment days. Radiation (2Gy) was delivered daily, 5 days per week for 2 weeks. Mice were sacrificed one week after treatment completion for analysis.

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Dosage form	50mg/kg; oral gavage; administered daily on radiation days (total 10 doses over 2 weeks).
Applications	M3814 combined with SOC significantly increased the clinical complete response rate compared to SOC alone. no significant difference in pathological complete response was observed between SOC plus M3814 and SOC alone. M3814 effectively inhibited DNA-PK phosphorylation in tumors when combined with SOC treatment.

References:

[1] Wu ZX, Peng Z, Yang Y, et al. M3814, a DNA-PK Inhibitor, Modulates ABCG2-Mediated Multidrug Resistance in Lung Cancer Cells. Front Oncol. 2020 May 12;10:674.

[2] Smithson M, Irwin RK, Williams G, et al. Inhibition of DNA-PK may improve response to neoadjuvant chemoradiotherapy in rectal cancer. Neoplasia. 2022 Mar;25:53-61.

Background

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M3814 (nedisertib) is a novel, orally active DNA-dependent protein kinase (DNA-PK) inhibitor. M3814 blocks the DNA damage repair pathway by inhibiting DNA-PK activity[1-2]. M3814 enhances the accumulation of DNA double-strand breaks, thereby increasing tumor cell sensitivity to radiotherapy. M3814 is primarily used in studies related to solid tumors and combination therapy with radiation[3-4].

In vitro, U251 glioblastoma cell lines were treated with M3814 (30-1000nM) for 24 hours, followed by ionizing radiation. When the concentration was greater than 300nM, M3814 significantly inhibited DNA-PKcs autophosphorylation, enhanced radiation-induced cell killing effects, and delayed the disappearance of γH2AX foci[5]. In non-small cell lung cancer NCI-H460/MX20 and A549/MX10 cell lines, pretreatment with M3814 (0.3-1μM) for 2 hours, followed by incubation with anticancer drugs for 72 hours, M3814 inhibited the ABCG2 efflux pump function, increased the intracellular accumulation of anticancer drugs[6].

In vivo, normal FVB mice underwent hemibrain irradiation (30Gy in 5 fractions) followed by a single oral dose of M3814 (60mg/kg) administered 10 minutes after irradiation. Drug distribution was measured at 2 and 5 hours post-irradiation, and radiation failed to effectively enhance the distribution of M3814 within the tumors[7]. In a BALB/c mouse model with subcutaneous CT26 colorectal cancer xenografts, oral administration of M3814 (50mg/kg) combined with standard of care (SOC) (Capecitabine 100mg/kg and 2Gy irradiation; 5 times per week for 2 weeks), M3814 significantly improved the clinical complete response rate compared to SOC alone. However, no significant difference in pathological complete response was observed between SOC plus M3814 and SOC alone[8].

References:
[1] Wise HC, Iyer GV, Moore K, et al. Activity of M3814, an Oral DNA-PK Inhibitor, In Combination with Topoisomerase II Inhibitors in Ovarian Cancer Models. Sci Rep. 2019 Dec 11;9(1):18882.
[2] Christner SM, Parise RA, Bakkenist CJ, et al. Quantitation of the DNA-dependent protein kinase inhibitor peposertib (M3814) and metabolite in human plasma by LC-MS/MS. Biomed Chromatogr. 2024 Dec;38(12):e6024.
[3] Zenke FT, Zimmermann A, Sirrenberg C, et al. Pharmacologic Inhibitor of DNA-PK,

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M3814, Potentiates Radiotherapy and Regresses Human Tumors in Mouse Models. Mol Cancer Ther. 2020 May;19(5):1091-1101.
[4] Wang M, Chen S, Wei Y, et al. DNA-PK inhibition by M3814 enhances chemosensitivity in non-small cell lung cancer. Acta Pharm Sin B. 2021 Dec;11(12):3935-3949.
[5] Dragojevic S, Smith EJ, Regan MS, et al. DNA-PK Inhibition Shows Differential Radiosensitization in Orthotopic GBM PDX Models Based on DDR Pathway Deficits. Mol Cancer Ther. 2025 Jun 4;24(6):859-869.
[6] Wu ZX, Peng Z, Yang Y, et al. M3814, a DNA-PK Inhibitor, Modulates ABCG2-Mediated Multidrug Resistance in Lung Cancer Cells. Front Oncol. 2020 May 12;10:674.
[7] Zhang W, Grams MP, Oberoi RK, et al. The impact of therapeutic radiation on drug distribution across the blood-brain barrier in normal mouse brain and orthotopic glioblastoma tumors. Neuro Oncol. 2025 Oct 14;27(9):2250-2261.
[8] Smithson M, Irwin RK, Williams G, et al. Inhibition of DNA-PK may improve response to neoadjuvant chemoradiotherapy in rectal cancer. Neoplasia. 2022 Mar;25:53-61.

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