# VX-984

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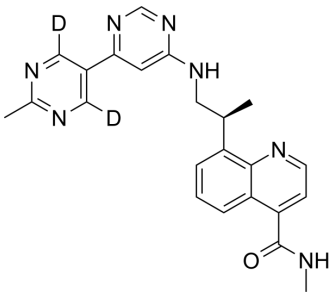
| **Cat. No.:** | HY-19939S |
| **CAS No.:** | 1476074-39-1 |
| **Molecular Formula:** | $C_{23}H_{21}D_2N_7O$ |
| **Molecular Weight:** | 415.49 |
| **Target:** | DNA-PK |
| **Pathway:** | Cell Cycle/DNA Damage; PI3K/Akt/mTOR |
| **Storage:** | Powder -20°C 3 years<br>4°C 2 years<br>In solvent -80°C 2 years<br>-20°C 1 year |



## SOLVENT & SOLUBILITY

**In Vitro**

DMSO : 10 mg/mL (24.07 mM; Need ultrasonic)

| Preparing Stock Solutions | Solvent / Mass / Concentration | 1 mg | 5 mg | 10 mg |
|---|---|---|---|---|
| | 1 mM | 2.4068 mL | 12.0340 mL | 24.0680 mL |
| | 5 mM | 0.4814 mL | 2.4068 mL | 4.8136 mL |
| | 10 mM | 0.2407 mL | 1.2034 mL | 2.4068 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: ≥ 1 mg/mL (2.41 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 1 mg/mL (2.41 mM); Clear solution

## BIOLOGICAL ACTIVITY

**Description**

VX-984 is an orally active, potent, selective and BBB-penetrated DNA-PK inhibitor. VX-984 efficiently inhibits NHEJ (non-homologous end joining) and increases DSBs (DNA double-strand breaks). VX-984 can be used for glioblastomas (GBM) and non-small cell lung cancer (NSCLC) research. VX-984 is a de novo deuterium[1][2][3].

**In Vitro**

VX-984 (0-500 nM, 30 min) inhibits radiation-induced DNA-PKcs phosphorylation in U251 and NSC11 cells[1].
VX-984 (0-500 nM) enhances the radiosensitivity of U251 and NSC11 cells in a concentration-dependent manner[1].
VX-984 inhibits the repair of radiation-induced DNA double-strand breaks (DSBs)[1].
VX-984 (0-1 μM) increases alternate pathways of DSB repair, including HR (homologous recombination) and mutagenic NHEJ (mNHEJ)[2].
Stable heavy isotopes of hydrogen, carbon, and other elements have been incorporated into drug molecules, largely as

tracers for quantitation during the drug development process. Deuteration has gained attention because of its potential to affect the pharmacokinetic and metabolic profiles of drugs[4].
Potential advantages of deuterated compounds:
(1) Extend the half-life in vivo. Deuterated compounds may be able to prolong the pharmacokinetic characteristics of the compound, that is, prolong the half-life in vivo. This can improve compound safety, efficacy and tolerability, and increase ease of administration.
(2) Improve oral bioavailability. Deuterated compounds may reduce the degree of unwanted metabolism (first-pass metabolism) in the gut wall and liver, allowing a greater proportion of the unmetabolized drug to reach its target site of action. High bioavailability determines its activity at low doses and better tolerance.
(3) Improve metabolic characteristics. Deuterated compounds may reduce the formation of toxic or reactive metabolites and improve drug metabolism.
(4) Improve drug safety. Deuterated compounds may reduce or eliminate adverse side effects of pharmaceutical compounds and are safe.
(5) Preserve the therapeutic properties. Deuterated compounds are expected to retain similar biochemical potency and selectivity to hydrogen analogs in previous studies.

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: | U251 and NSC11 cells |
| Concentration: | 0, 100, 250, and 500 nM |
| Incubation Time: | 30 min |
| Result: | Showed a concentration-dependent decrease in radiation-induced DNA-PKcs phosphorylation in each glioma line, when VX-984 was delivered 1 hour before irradiation. VX-984 treatment alone had no effect. |

**In Vivo**

VX-984 (0-100 mg/kg, Oral gavage, daily) inhibits radiation-induced DNA-PKcs phosphorylation in orthotopic brain tumor xenografts[1].
VX-984 (0-50 mg/kg, Oral gavage, twice a day for 2 days) enhances the radiosensitivity of brain tumor xenografts[1].

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

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| Animal Model: | Athymic female nude mice (6-8 weeks old, 7-8 mice/group, U251 intracerebral xenografts) [1] |
| Dosage: | 0, 50, and 100 mg/kg |
| Administration: | Oral gavage, daily, 1 or 4 hours before irradiation (10 Gy) |
| Result: | Reduced the levels DNA-PKcs phosphorylation after irradiation. |

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| Animal Model: | Athymic female nude mice (6-8 weeks old, 7 mice/group, U251 intracerebral xenografts)[1] |
| Dosage: | 0, 50 mg/kg |
| Administration: | Oral gavage, twice a day, 30 minutes before and 4 hours following local irradiation of the tumor (3 Gy) for 3 consecutive days (3×3 Gy) |
| Result: | VX-984 treatment of U251 tumors alone had no significant effect on overall survival as compared with vehicle; radiation alone resulted in an increase in survival. VX-984 and radiation combination protocol increased tumor radiosensitivity, and significantly increased the survival of mice compared with radiation alone. |

## CUSTOMER VALIDATION

- Nat Biotechnol. 2023 Aug 3.
- Nat Commun. 2023 Sep 6;14(1):5474.
- Cell Death Dis. 2020 Jul 30;11(7):602.
- Transl Oncol. 2020 Nov;13(11):100834.

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## REFERENCES


[1]. Timme CR, et al. The DNA-PK Inhibitor VX-984 Enhances the Radiosensitivity of Glioblastoma Cells Grown In Vitro and as Orthotopic Xenografts. Mol Cancer Ther. 2018 Jun;17(6):1207-1216.

[2]. Khan AJ, et al. VX-984 is a selective inhibitor of non-homologous end joining, with possible preferential activity in transformed cells. Oncotarget. 2018 May 25;9(40):25833-25841.

[3]. Diane Boucher, et al. Abstract 3716: Potent radiation enhancement with VX-984, a selective DNA-PKcs inhibitor for the treatment of NSCLC. Cancer Res (2016) 76 (14_Supplement): 3716.

[4]. Russak EM, et al. Impact of Deuterium Substitution on the Pharmacokinetics of Pharmaceuticals. Ann Pharmacother. 2019 Feb;53(2):211-216.





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