

Product Data Sheet

Product Name: BDP9066

Cat. No.: GC33340

Chemical Properties

Cas. No. 2226507-04-4

SMILES C12=C(N3CCC[C@@]4(CCCCN4)C3)C=CNC1=NC=C2C5=NC=NC=C5

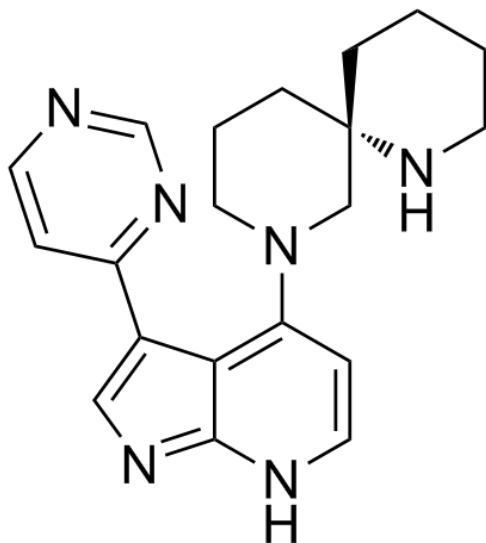
Formula $C_{20}H_{24}N_6$ M.Wt 348.44

Solubility Soluble in DMSO Storage Store at -20°C

General tips For obtaining a higher solubility, please warm the tube at 37 °C and shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C 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



Protocol

Cell experiment [1]:

Cell lines E2 and G7 cell lines

Caution: Product has not been fully validated for medical applications. For research use only.

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Cells were plated onto 6-well plates in triplicate per biological repeat. Twenty-four hours after plating, cells were treated with DMSO or 250µmol/L BDP9066 Preparation Method for 2 hours, followed by radiation treatment and media replacement. Cells were fixed after 2 to 3 weeks, stained with crystal violet, and colonies counted manually. Data were fitted using a linear quadratic model.

Reaction

Conditions 250µM; 2h

Applications

BDP9066 treatment disrupts the actin-myosin cytoskeleton, inducing an aberrant morphology that inhibits migration.

Animal experiment [1]:

Animal models

Mice bearing U87MG or G7 intracranial tumors

Preparation Method

To test the efficacy of BDP9066 in inhibiting radiation-induced invasion in vivo, we established G7 intracranial tumors in four cohorts of mice: vehicle, BDP9066, RT + vehicle, and RT + BDP9066. Mice underwent T2-weighted MRI to confirm the presence and equivalence of size of tumors 11 weeks after tumor cell injection; treatment was commenced the following week. Mice in the RT cohorts received 3 × 2Gy whole brain RT over the course of 1 week. Twice-daily dosing of vehicle or BDP9066 was initiated at the same time as RT and continued for 10 days before sacrifice of the animals to ensure sustained inhibition of MRCK. Twice-daily dosing was chosen because, although the PK profile of BDP9066 showed good bioavailability, rapid clearance was also observed. A transient vasodilatory effect lasting 20 to 30 minutes was noted in some animals as evidenced by reddening of the ears.

Dosage form

5mg/kg; twice daily, monday to friday, 4 weeks; subcutaneous injection

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Applications

Increased numbers of GBM cells were observed in the contralateral hemispheres of mice in the “irradiated + vehicle” cohort. Importantly, irradiated mice that were treated with BDP9066 showed no increase of tumor cell infiltration to the contralateral hemisphere. BDP9066 penetrates intracranial GBM xenografts and inhibits radiation-induced infiltration of GBM cells in vivo.

References:

[1]. Birch J L, Strathdee K, Gilmour L, et al. A novel small-molecule inhibitor of MRCK prevents radiation-driven invasion in glioblastoma[J]. Cancer research, 2018, 78(22): 6509-6522.

Background

BDP9066 is a selective inhibitor of myotonic dystrophy-associated Cdc42-binding kinase (MRCK), with an IC_{50} of 64nM for MRCK β and K_i values of 0.0136nM and 0.0233nM for MRCK α/β in SCC12 cells^[1]. MRCK is a protein kinase that acts downstream of Cdc42. After being activated by Cdc42, MRCK promotes actin polymerization, stress fiber formation and cell membrane binding by phosphorylating downstream molecules such as myosin light chain 2 (MLC2), LIM domain kinase (LIMK), and myosin phosphatase target 1 (MYPT1)^[2]. BDP9066 can be applied to the study of triple-negative breast cancer (TNBC), high-grade serous ovarian carcinoma (HGSC), and glioblastoma (GBM), and is a potential cancer chemotherapy drug^[3].

In vitro, treatment of E2 and G7 cell lines with 250 μ M BDP9066 for 2 hours disrupted the actin-myosin cytoskeleton, inducing abnormal cell morphology to inhibit migration^[4]. Treatment of HGSOC cells with 1 μ M BDP9066 for 24 hours increased the level of cleaved PARP in the cells, inhibited cell growth, induced apoptosis, and inhibited local adhesion signals, thereby impairing the globular formation of HGSOC cells^[5]. In in vitro kinase assays, the EC_{50} values of BDP9066 for MRCK α and MRCK β were 65nM and 72nM, respectively^[5].

In vivo, when FVB mice were treated with BDP9066 (50 μ L; 80% (v/v) in DMSO; administered 4 times over 2 days) through skin application, the drug level in the skin of the mice was significantly higher than that in the blood, and the total tumor volume and mean papillary volume were significantly reduced, but the total number of papillomas was not different from that in the control group^[1]. When

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mice carrying U87MG or G7 intracranial tumors were treated with BDP9066 (5mg/kg; twice daily; Monday to Friday; 4 weeks; subcutaneous injection), the tumor cell infiltration in the contralateral hemisphere of the irradiated mice treated with BDP9066 was not increased compared with the increase in the number of GBM cells in the contralateral hemisphere of the control mice after irradiation with 3×2 Gy^[4].

References:

- [1]. Unbekandt M, Belshaw S, Bower J, et al. Discovery of potent and selective MRCK inhibitors with therapeutic effect on skin cancer[J]. Cancer research, 2018, 78(8): 2096-2114.
- [2]. Yamaguchi H, Chang L C, Chang O S S, et al. MRCK as a potential target for claudin-low subtype of breast Cancer[J]. International Journal of Biological Sciences, 2024, 20(1): 1.
- [3]. McKinnon H J, Birch J, McDonald L, et al. A novel small molecule inhibitor of MRCK shows utility in blocking radiation induced invasion of glioblastoma cells in vitro and in vivo[J]. Cancer Research, 2018, 78(13_Supplement): 1933-1933.
- [4]. Birch J L, Strathdee K, Gilmour L, et al. A novel small-molecule inhibitor of MRCK prevents radiation-driven invasion in glioblastoma[J]. Cancer research, 2018, 78(22): 6509-6522.
- [5]. Kurimchak A M, Herrera-Montávez C, Brown J, et al. Functional proteomics interrogation of the kinome identifies MRCKA as a therapeutic target in high-grade serous ovarian carcinoma[J]. Science signaling, 2020, 13(619): eaax8238.

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