

Product Data Sheet

Product Name: Midostaurin (PKC412)

Cat. No.: GC10496

Chemical Properties

Cas. No. 120685-11-2

SMILES CC12C(C(CC(O1)N3C4=CC=CC=C4C5=C6C(=C7C8=CC=CC=C8N2C7=C53)CNC6=O)N(C)C(=O)C9=CC=CC=C9)OC

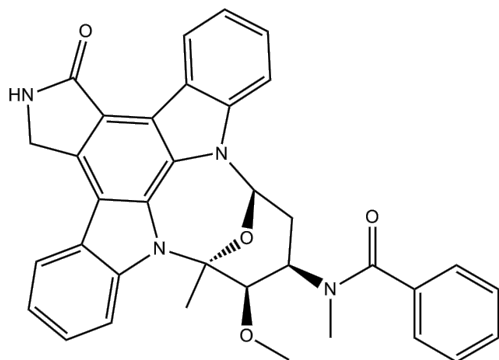
Formula $C_{35}H_{30}N_4O_4$ M.Wt 570.64

Solubility ≥ 57.1 mg/mL in DMSO with ultrasonic 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 Peripheral blood mononuclear cells (PBMCs)

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

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PBMCs were cultured in Roswell Park Memorial Institute 1640 1x (RPMI) medium supplemented with 20% fetal bovine serum (FBS). In addition, PBMCs were treated with IL-2 (5ng/mL) and IL-7 (10ng/mL), as well as 1μM of Midostaurin. PBMCs were seeded at 2 million cells per well in a 6 well plate, and allowed to incubate at 5% CO₂, 37 °C for 72 hours before analysis via flow cytometry or quantitative polymerase chain reaction.

Reaction Conditions 1μM; 72h

Applications Midostaurin reduces CD4 + CD25 + FOXP3 + T cell population in healthy PBMC.

Animal experiment [2]:

Animal models CT26 cells xenograft tumor mouse model

Male BALB/c mice at five weeks old were purchased from the National Laboratory Animal Center of Taiwan and housed under 12-h light/dark cycle under a specific pathogen-free facility. The 4×10^6 CT26 cells in 100μL PBS were subcutaneously inoculated on the right hindlimb of the mice. After the tumors grew for 7 days to achieve a mean diameter of approximate 5mm, mice were randomly allocated into 4 groups as follows: (1) control, (2) Midostaurin (100mg/kg), (3) intraperitoneal anti-PD-1 injection (200μg), and (4) Midostaurin in combination with anti-PD-1.

Dosage form 100mg/kg; po; 7d

Applications Midostaurin treatment significantly inhibited tumor growth.

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References:

- [1]. Gutierrez L, Jang M, Zhang T, et al. Midostaurin reduces regulatory T cells markers in acute myeloid leukemia[J]. Scientific reports, 2018, 8(1): 17544.
- [2]. Lai C T, Chi C W, Wu S H, et al. Midostaurin modulates tumor microenvironment and enhances efficacy of anti-PD-1 against colon cancer[J]. Cancers, 2022, 14(19): 4847.

Background

Midostaurin (PKC412) is an oral, multi-targeted tyrosine kinase inhibitor that inhibits multiple kinases, including FLT3, KIT, PDGFR, and VEGFR (IC_{50} = 22-500nM) [1-2]. Midostaurin competitively inhibits the binding of ATP to kinases, thereby blocking tumor cell proliferation and promoting apoptosis [3]. Midostaurin is commonly used to treat acute myeloid leukemia (AML) harboring FLT3 mutations [4].

In peripheral blood mononuclear cells (PBMCs), Midostaurin (1 μ M; 72h) significantly reduced the CD4+CD25+FOXP3+ T cell population and FOXP3 mRNA expression in PBMCs [5]. In MDA -MB-468 cells, Midostaurin (1 μ M; 72h) directly inhibits Aurora kinases A and B and subsequently reduces cell viability in TNBC cells [6]. In HMC-1 cells, ponatinib cooperates with Midostaurin (0-0.1 μ M; 48h) to induce growth inhibition and apoptosis [7].

In CT26 cells xenograft tumor mouse model, Midostaurin (100mg/kg; po; 7d) treatment significantly inhibited tumor growth [8]. In HL-60 cells xenograft tumor mouse model, All-trans retinoic acid combined with Midostaurin (50mg/kg; po; 10d) treatment significantly inhibited tumor growth [9].

References:

- [1]. Fabbro D, Buchdunger E, Wood J, et al. Inhibitors of protein kinases: CGP 41251, a protein kinase inhibitor with potential as an anticancer agent[J]. Pharmacology & therapeutics, 1999, 82(2-3): 293-301.
- [2]. Fabbro D, Ruetz S, Bodis S, et al. PKC412-a protein kinase inhibitor with a broad therapeutic potential[J]. Anti-cancer drug design, 2000, 15(1): 17-28.
- [3]. Gallogly M M, Lazarus H M, Cooper B W. Midostaurin: a novel therapeutic agent for patients with FLT3-mutated acute myeloid leukemia and systemic mastocytosis[J]. Therapeutic advances in hematology, 2017, 8(9): 245-261.

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- [4]. Levis M. Midostaurin approved for FLT3-mutated AML[J]. Blood, The Journal of the American Society of Hematology, 2017, 129(26): 3403-3406.
- [5]. Gutierrez L, Jang M, Zhang T, et al. Midostaurin reduces regulatory T cells markers in acute myeloid leukemia[J]. Scientific reports, 2018, 8(1): 17544.
- [6]. Kawai M, Nakashima A, Kamada S, et al. Midostaurin preferentially attenuates proliferation of triple-negative breast cancer cell lines through inhibition of Aurora kinase family[J]. Journal of biomedical science, 2015, 22(1): 48.
- [7]. Gleixner K V, Peter B, Blatt K, et al. Synergistic growth-inhibitory effects of ponatinib and midostaurin (PKC412) on neoplastic mast cells carrying KIT D816V[J]. Haematologica, 2013, 98(9): 1450.
- [8]. Lai C T, Chi C W, Wu S H, et al. Midostaurin modulates tumor microenvironment and enhances efficacy of anti-PD-1 against colon cancer[J]. Cancers, 2022, 14(19): 4847.
- [9]. Lu H, Weng X, Sheng Y, et al. Combination of midostaurin and ATRA exerts dose-dependent dual effects on acute myeloid leukemia cells with wild type FLT3[J]. BMC cancer, 2022, 22(1): 749.

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