

Product Data Sheet

Product Name: AMG 925

Cat. No.: GC14974

Chemical Properties

Cas. No. 1401033-86-0

SMILES C[C@H]1CC[C@H](N2C3=CN=CC=C3C4=CN=C(NC5=NC6=C(CN(C(CO)=O)CC6)C=C5)N=C24)CC1

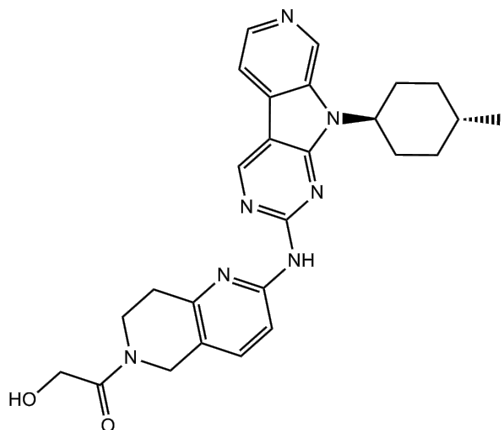
Formula C₂₆H₂₉N₇O₂ M.Wt 471.55

Solubility <0.94mg/mL 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 HL60 cells (human acute myeloid leukemia cell line)

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Preparation Method HL60 cells were maintained in RPMI-1640 medium supplemented with 10% fetal bovine serum (FBS) and 1% Antibiotic-Antimycotic at 37°C, 5% CO₂, with sub-culture performed when cell density reached 5×10⁵ cells/mL to maintain logarithmic growth. For MTT cytotoxicity assay, HL60 cells were seeded in 96-well plates at 5×10⁴ cells/well, and treated with AMG 925 at gradient concentrations of 0, 6.25, 12.5, 25, 50 and 100nM for 24h; for combination assay, AMG 925 was co-treated with HAA2020 at a ratio of HAA2020:AMG 925 = 50:1 for 24h.

Reaction Conditions 0-100nM; 24h

Applications AMG 925 showed dose-dependent cytotoxic activity against HL60 cells, with a 24h IC₅₀ of 54.4±7.7nM. The combination of AMG 925 and HAA2020 presented antagonistic effect, with a combination index (CI) >1 at Fa=0.9, and the combination IC₅₀ was 3355±347.8nM.

Animal experiment [2]:

Animal models CrTac:NCR-Foxn1nu (NCR) nude mice bearing MOLM13 xenograft

Preparation Method NCR nude mice were intraperitoneally injected with 100μL anti-asialo GM1 antibody to deplete NK activity. The following day, 7.5 × 10⁶ MOLM13 cells formulated as a 1:1 mixture with Matrigel in PBS were subcutaneously inoculated into the right flank. When tumors were established, mice were orally gavaged with AMG 925 once daily for 8 days. Tumors were measured every other day, and body weights were recorded. At the end of the study, tumors were harvested for analysis of STAT5 and Rb phosphorylation.

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Dosage form 25-150mg/kg; p.o.; once daily for 8 days

Applications AMG 925 produced dose-dependent inhibition of MOLM13 tumor growth, with ED₅₀ of 22mg/kg corresponding to an AUC of 28μM·h. Phosphorylation of STAT5 and Rb in tumor tissues was significantly reduced compared with vehicle treatment. Body weight loss remained within 10% throughout the study, and AMG 925 was well tolerated.

References:

- [1] Abdalla AN, Abdallah ME, Aslam A, et al. Synergistic Anti Leukemia Effect of a Novel Hsp90 and a Pan Cyclin Dependent Kinase Inhibitors. *Molecules*. 2020 May 8;25(9):2220.
- [2] Li Z, Wang X, Eksterowicz J, et al. Discovery of AMG 925, a FLT3 and CDK4 dual kinase inhibitor with preferential affinity for the activated state of FLT3. *J Med Chem*. 2014 Apr 24;57(8):3430-49.

Background

AMG 925 is an orally active dual FLT3 and CDK4 kinase inhibitor (IC₅₀=1nM and 3nM). AMG 925 can be used for the study of acute myeloid leukemia (AML) and related resistance mechanisms^[1-4].

In vitro, AMG 925 (0–100nM) was applied to HL60 cells for 24 hours. AMG 925 significantly inhibited cell proliferation with an IC₅₀ of 54.4 ± 7.7nM^[5]. AMG 925 (0.1nM–1μM) was applied to MOLM13, MV4-11, and other FLT3 internal tandem duplication (ITD)-mutated AML cells for 3 days. AMG 925 inhibited cell proliferation and STAT5 phosphorylation, suppressed RB phosphorylation, and induced apoptosis^[6].

In vivo, AMG 925 (12.5–37.5mg/kg; twice daily; 6-hour interval) was orally administered to CrTac:NCR-Foxn1nu nude mice bearing subcutaneous xenografts and to NOD/SCID IL-2Rγ^{-/-} mice inoculated with MOLM13-Luc via tail vein for 10 days. AMG 925 inhibited subcutaneous and systemic xenograft growth and reduced P-STAT5 and P-RB levels in bone marrow tumor cells^[7]. AMG 925 (25–150mg/kg; once daily) was orally administered to NCR nude mice bearing MOLM13 subcutaneous xenografts for 8 days. AMG 925 produced dose-dependent tumor growth inhibition

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and reduced STAT5 and Rb phosphorylation levels in MOLM13 tumor tissues^[8].

References:

- [1] Wu M, Li C, Zhu X. FLT3 inhibitors in acute myeloid leukemia. J Hematol Oncol. 2018 Dec 4;11(1):133.
- [2] Smith CC, Viny AD, Massi E, et al. Recurrent Mutations in Cyclin D3 Confer Clinical Resistance to FLT3 Inhibitors in Acute Myeloid Leukemia. Clin Cancer Res. 2021 Jul 15;27(14):4003-4011.
- [3] Liu GH, Chen T, Zhang X, et al. Small molecule inhibitors targeting the cancers. MedComm (2020). 2022 Oct 13;3(4):e181.
- [4] Yuan K, Wang X, Dong H, et al. Selective inhibition of CDK4/6: A safe and effective strategy for developing anticancer drugs. Acta Pharm Sin B. 2021 Jan;11(1):30-54.
- [5] Abdalla AN, Abdallah ME, Aslam A, et al. Synergistic Anti Leukemia Effect of a Novel Hsp90 and a Pan Cyclin Dependent Kinase Inhibitors. Molecules. 2020 May 8;25(9):2220.
- [6] Li C, Liu L, Liang L, et al. AMG 925 is a dual FLT3/CDK4 inhibitor with the potential to overcome FLT3 inhibitor resistance in acute myeloid leukemia. Mol Cancer Ther. 2015 Feb;14(2):375-83.
- [7] Keegan K, Li C, Li Z, et al. Preclinical evaluation of AMG 925, a FLT3/CDK4 dual kinase inhibitor for treating acute myeloid leukemia. Mol Cancer Ther. 2014 Apr;13(4):880-9.
- [8] Li Z, Wang X, Eksterowicz J, et al. Discovery of AMG 925, a FLT3 and CDK4 dual kinase inhibitor with preferential affinity for the activated state of FLT3. J Med Chem. 2014 Apr 24;57(8):3430-49.

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