

Product Data Sheet

Product Name: RMC-4550

Cat. No.: GC33044

Chemical Properties

Cas. No. 2172651-73-7

SMILES ClC1=C(C(C2=NC(CO)=C(N=C2C)N3CCC4(CC3)CO[C@H]([C@H]4N)C)=CC=C1)Cl

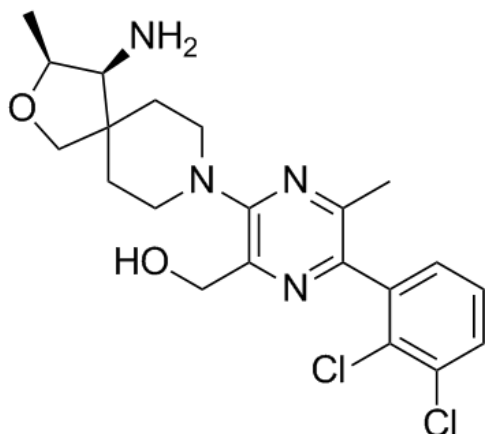
Formula $C_{21}H_{26}Cl_2N_4O_2$ M.Wt 437.36

Solubility DMSO : 125 mg/mL (285.81 mM) 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 Molm-14, MV4-11, Kasumi-1, and SKNO-1 (human acute myeloid leukemia cell lines with FLT3 or KIT mutations)

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The indicated AML cell lines were cultured in RPMI-1640 medium supplemented with 10% fetal bovine serum (FBS) and 1% penicillin/streptomycin/L-glutamine. Kasumi-1 cells were cultured with 20% FBS. The culture medium for the SKNO-1 cell line was supplemented with human GM-CSF (10ng/mL). Cells were treated with the RMC-4550.

Reaction Conditions
500nM; 24-48h.

Applications
RMC-4550 inhibited cell proliferation, impaired RAS GTP loading, and repressed downstream phosphorylation of ERK. RMC-4550 increased the expression of the pro-apoptotic protein BMF and decreased levels of the anti-apoptotic protein MCL1. Treatment with RMC-4550 increased apoptotic priming and dependency on BCL2.

Animal experiment [2]:

Animal models Female Balb/c nude mice

Preparation Method Mice were subcutaneously injected with RPMI-8226 cells. When tumors reached approximately 100-130mm³, tumor-bearing mice were randomly divided into cohorts and received RMC-4550 (30mg/kg; p.o.) or vehicle for 35 days.

Dosage form 30mg/kg; p.o.; daily for 35 days.

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Applications Oral administration of RMC-4550 reduced tumor size, growth, and weight in the xenograft mice compared to the vehicle-treated group. Tumor masses from the RMC-4550 treated mice exhibited increased expression of BAK, P21, and cleaved caspase-3, and decreased levels of p-SHP2 and p-ERK.

References:

- [1] Popescu B, Stahlhut C, Tarver TC, et al. Allosteric SHP2 inhibition increases apoptotic dependency on BCL2 and synergizes with venetoclax in FLT3- and KIT-mutant AML. *Cell Rep Med*. 2023 Nov 21;4(11):101290.
- [2] Zhou P, Xiao M, Li W, et al. SHP2 Inhibitors Show Anti-Myeloma Activity and Synergize With Bortezomib in the Treatment of Multiple Myeloma. *Front Pharmacol*. 2022 Apr 6;13:841308.

Background

RMC-4550 is an orally active allosteric inhibitor of SHP2 ($IC_{50}=0.583nM$). RMC-4550 disrupts the SHP2/SOS1/GRB2 module by stabilizing the autoinhibited conformation of the wild-type SHP2 enzyme, thereby downregulating RAS-GTP levels and inhibiting the RAS/MAPK signaling pathway^[1-2]. RMC-4550 can be used in research related to KRAS-mutant pancreatic cancer, lung cancer, and esophageal cancer, among others^[3-4].

In vitro, FLT3-ITD-mutant AML cell lines (Molm-14, MV4-11) and KIT-mutant cell lines (SKNO-1) were treated with RMC-4550 (500nM) for 24-48 hours. RMC-4550 upregulated the expression of interferon-stimulated genes, including IFIT2, OAS1, and OASL, inhibited cell proliferation, induced apoptosis, and reduced RAS-GTP levels and ERK phosphorylation^[5]. Treatment of neuroblastoma cell lines (CLB-GE, CLB-GA, CLB-BA, KELLY, and SK-N-AS) with RMC-4550 (0.1-1000nM) for 72 hours inhibited cell proliferation in a dose-dependent manner^[6].

In vivo, Balb/c nude mice with subcutaneous RPMI-8226 cell-derived tumors were orally administered RMC-4550 (30mg/kg) once daily for 20 days. RMC-4550 significantly inhibited the growth of myeloma xenograft tumors^[7]. C57BL/6J or nu/nu mice, which received orthotopic inoculation of LLC 46 NRAS KO or mKRC.1 cells into the left lung, were orally administered RMC-4550 (30mg/kg) once daily for 35 days. RMC-4550 monotherapy slightly slowed the growth of LLC 46

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NRAS KO tumors, and its combination with MRTX-849 caused tumor regression; in mKRC.1 tumors, RMC-4550 monotherapy was ineffective, but its combination with MRTX-849 produced sustained tumor regression^[8].

References:

- [1] Nichols RJ, Haderk F, Stahlhut C, et al. RAS nucleotide cycling underlies the SHP2 phosphatase dependence of mutant BRAF-, NF1- and RAS-driven cancers. Nat Cell Biol. 2018 Sep;20(9):1064-1073.
- [2] Frank KJ, Mulero-Sánchez A, Berninger A, et al. Extensive preclinical validation of combined RMC-4550 and LY3214996 supports clinical investigation for KRAS mutant pancreatic cancer. Cell Rep Med. 2022 Nov 15;3(11):100815.
- [3] Wang RR, Liu WS, Zhou L, et al. Probing the acting mode and advantages of RMC-4550 as an Src-homology 2 domain-containing protein tyrosine phosphatase (SHP2) inhibitor at molecular level through molecular docking and molecular dynamics. J Biomol Struct Dyn. 2020 Mar;38(5):1525-1538.
- [4] Vemulapalli V, Donovan KA, Seegar TCM, et al. Targeted Degradation of the Oncogenic Phosphatase SHP2. Biochemistry. 2021 Aug 31;60(34):2593-2609.
- [5] Popescu B, Stahlhut C, Tarver TC, et al. Allosteric SHP2 inhibition increases apoptotic dependency on BCL2 and synergizes with venetoclax in FLT3- and KIT-mutant AML. Cell Rep Med. 2023 Nov 21;4(11):101290.
- [6] Uçkun E, Siaw JT, Guan J, et al. BioID-Screening Identifies PEAK1 and SHP2 as Components of the ALK Proximitome in Neuroblastoma Cells. J Mol Biol. 2021 Sep 17;433(19):167158.
- [7] Zhou P, Xiao M, Li W, et al. SHP2 Inhibitors Show Anti-Myeloma Activity and Synergize With Bortezomib in the Treatment of Multiple Myeloma. Front Pharmacol. 2022 Apr 6;13:841308.
- [8] Sisler DJ, Hinz TK, Le AT, et al. Evaluation of KRASG12C inhibitor responses in novel murine KRASG12C lung cancer cell line models. Front Oncol. 2023 Feb 8;13:1094123.

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