

Product Data Sheet

Product Name: RMC-6236

Cat. No.: GC92066

Chemical Properties

Cas. No. 2765081-21-6

Chemical Name (1S,2S)-N-[(2R,14S,18S)-1-ethyl-18,19,20,21-tetrahydro-2-[2-[(1S)-1-methoxyethyl]-5-(4-methyl-1-piperazinyl)-3-pyridinyl]-25,25-dimethyl-15,22-dioxo-17H-5,3-([4,2]-endo-thiazolopropano[1,3]-endo-pyridazinomethanoxypyrano)-1H-indol-14-yl]-2-methyl-cyclopropanecarboxamide

SMILES O=C([C@H](CCC1)NN1C([C@H](CC2=NC3=CS2)NC([C@H]4C[C@@H]4C)=O)=O)OCC(C)(C)CC5=[C@@]([C@@]6=C([C@H](C)OC)N=CC(N7CCN(C)CC7)=C6)N(CC)C8=C5C=C3C=C8

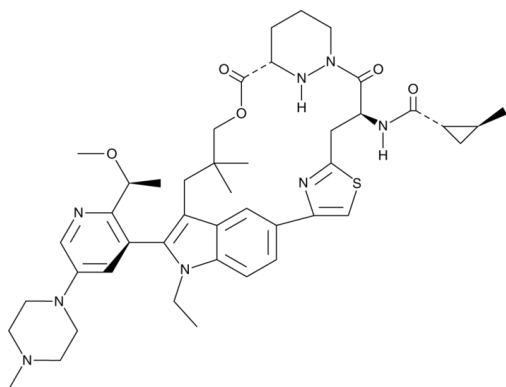
Formula $C_{44}H_{58}N_8O_5S$ M.Wt 811.1

Solubility DMSO: >100mg/ml Storage -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]:

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Cell lines	GP2D cells
Preparation Method	10nM RMC-6236 for 0, 4, 24, or 48 hours in the presence or absence of 1 μ M KO-2806. Evaluate the expression of mTOR pathway proteins.
Reaction Conditions	10nM; 0-48h
Applications	RMC-6236 was unable to durably inhibit mTOR activity, but the addition of KO-2806 controlled mTOR rebound.

Animal experiment [2]:

Animal models	Female BALB/c nude, NOD-SCID, and NMRI nu/nu mouse xenograft models.
Preparation Method	RMC-6236 was prepared using formulation of 10/20/10/60 (%v/v/v/v) DMSO/PEG-400/Solutol HS15/water. A single dose of RMC-6236 was administered orally at either 3, 10, or 25mg/kg. Blood and tissues, including the tumor, brain, colon, ear skin, and muscle, were harvested at indicated time points.
Dosage form	3, 10, 25mg/kg; once; p.o.
Applications	Dose-dependent blood and tumor exposure were observed following a single dose of RMC-6236 at 3, 10, or 25mg/kg. A single oral dose of 10 or 25mg/kg RMC-6236 was sufficient to achieve more than 95% inhibition (relative to vehicle control) of tumor DUSP6 levels at 8 hours after dose; the latter maintained >90% inhibition up to 24 hours after dose, diminishing thereafter in concordance with declining tumor RMC-6236 concentrations.

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References:

- [1] Patel H V, et al. The farnesyl transferase inhibitor KO-2806 re-sensitizes relapsing tumors to RAS inhibition. *BioRxiv*, 2024: 2024.12. 20.629824.
- [2] Jiang J, Jiang L, Maldonato BJ, et al. Translational and Therapeutic Evaluation of RAS-GTP Inhibition by RMC-6236 in RAS-Driven Cancers. *Cancer Discov.* 2024;14(6):994-1017.

Background

RMC-6236 is a reversible, GTP-binding RAS (ON) multi-selective inhibitor. RMC-6236 inhibits the active, GTP-bound state of both mutant and wild-type canonical RAS isoforms and has broad therapeutic potential in cancers driven by the RAS signaling pathway. RMC-6236 acts by forming a ternary complex: it first binds cyclophilin A (CypA; $K_d=55.3\text{nM}$) to form a binary complex, which then associates with RAS proteins, including KRAS (wild-type, G12V, and G12D), with K_d values of 131, 364, and 154nM, respectively^{[1][2]}.

In vitro, RMC-6236 significantly inhibits the growth of RAS-mutant cancer cell lines harboring KRAS G12X and NRAS Q61X mutations, with EC_{50} values of 8 and 22nM, respectively^[2]. Treatment of GP2D colorectal cancer cells with 10nM RMC-6236 for 4-48 hours did not sustain suppression of mTOR pathway activity, whereas combination with KO-2806 prevented its rebound^[3].

In vivo, a single oral gavage dose of RMC-6236 at 10 or 25mg/kg reduced tumor Dual Specificity Phosphatase 6 (DUSP6) levels by more than 95% at 8 hours and maintained more than 90% inhibition at 24 hours; at 25mg/kg, it also sustained more than 80% inhibition of pERK levels at 24 hours post-dose in mouse xenograft models^[2]. RMC-6236 administered orally at 10-25mg/kg once daily for 4 weeks showed dose-dependent antitumor activity in KRAS-mutant human tumor xenograft models, including Capan-2, NCI-H441, HPAC, and NCI-H358^[2]. RMC-6236, administered orally at 25mg/kg once daily for 28 days, inhibited tumor growth in xenograft models of *KRAS*^{G12C}-mutant NCI-H2122 non-small cell lung cancer and *KRAS*^{G12D}-mutant GP2D colorectal cancer^[3].

References:

- [1] Long SA, Amparo AM, Goodhart G, Ahmad SA, Waters AM. Evaluation of KRAS inhibitor-directed therapies for pancreatic cancer treatment. *Front Oncol.* 2024;14:1402128.

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- [2] Jiang J, Jiang L, Maldonato BJ, et al. Translational and Therapeutic Evaluation of RAS-GTP Inhibition by RMC-6236 in RAS-Driven Cancers. *Cancer Discov.* 2024;14(6):994-1017.
- [3] Patel H V, et al. The farnesyl transferase inhibitor KO-2806 re-sensitizes relapsing tumors to RAS inhibition. *BioRxiv*, 2024: 2024.12. 20.629824.

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