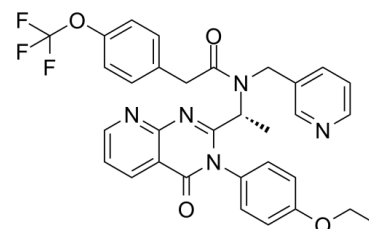


Data Sheet

Product Name:	AMG 487
Cat. No.:	CS-2662
CAS No.:	473719-41-4
Molecular Formula:	C ₃₂ H ₂₈ F ₃ N ₅ O ₄
Molecular Weight:	603.59
Target:	CXCR
Pathway:	GPCR/G Protein; Immunology/Inflammation
Solubility:	H ₂ O : < 0.1 mg/mL (insoluble); DMSO : ≥ 41 mg/mL (67.93 mM)



BIOLOGICAL ACTIVITY:

AMG 487 is an orally active and selective antagonist of CXC chemokine receptor 3 (**CXCR3**) which inhibits the binding of CXCL10 and CXCL11 to CXCR3 with IC₅₀s of 8.0 and 8.2 nM, respectively. IC₅₀ & Target: IC₅₀: 8.0 nM (¹²⁵I-IP-10 binding to CXCR3), 8.2 nM (¹²⁵I-ITAC binding to CXCR3) **In Vitro**: AMG 487 inhibits CXCR3-mediated cell migration by the three CXCR3 chemokines (IP-10 IC₅₀=8 nM, ITAC IC₅₀=15 nM, and MIG IC₅₀=36 nM). Furthermore, AMG 487 inhibits calcium mobilization in response to ITAC (IC₅₀=5 nM)^[1]. AMG487 (1 μM) develops into fewer lung metastases, and the lungs are significantly smaller than vehicle-treated lungs^[2]. AMG487 abrogates proliferation/survival of C26 tumour cells^[3]. **In Vivo**: AMG 487 (0.03-10 mg/kg, s.c.) exhibits significant reduction in cellular infiltration into the lungs in a dose dependent manner^[1]. AMG487 (5 mg/kg, s.c., twice daily) develops fewer metastases than that in vehicle-treated mice^[2]. AMG487 (5 mg/kg, s.c.)-treated mice exhibits fewer pulmonary nodules than the control mice in both the models. AMG487 reduces the tumour volume^[3].

PROTOCOL (Extracted from published papers and Only for reference)

Kinase Assay: ^[3]Cells are then lysed and sonicated in 50 mM Hepes pH 7.5, 150 mM NaCl, 20 mM EDTA, 1 mM PMSF, 10 μg/mL leupeptin, 2 μg/mL aprotinin and 0.2% NP-40. Equal amount of lysates are mixed in substrate buffer (50 mM Hepes, 100 mM NaCl, 1 mM EDTA, 10% sucrose, 0.5% CHAPS, 5 mM dithiothreitol) with Ac-DEVD-AMC substrate and caspase-3/7 substrate in a microtiter plate. Production of fluorogenic substrate is measured continuously at 37°C in a spectrophotometer Ascent Fluoroskan and the caspase activity (expressed as U/mg of protein) is defined as the amount of enzyme cleaving 1 nmol of substrate/min. **Cell Assay:** AMG 487 is prepared as a 10 mM stock with DMSO.^[3]Colon cancer cells are seeded at a density of 10⁴ cells cm² and incubated either in serum-enriched medium or in base medium (containing 0.1% bovine serum albumin, BSA) supplemented or not with various concentrations of rCXCL9, rCXCL10 and rCXCL11 for the indicated periods of time before being either trypsin-detached, collected and enumerated or re-fed with fresh medium for 3 days, harvested and enumerated. The morphology of the CRC cells is observed through an inverted optical microscope at ×20 magnification, and photographs are taken at day 7. **Animal Administration:** AMG487 is formulated in 20% of hydroxypropyl-β-cyclodextrin.^[2]Local tumor growth and spontaneous metastasis are evaluated by injecting 3×10⁵ viable tumor cells s.c. proximal to the right abdominal mammary gland of syngeneic female mice. Tumor diameters are measured by caliper twice weekly, and mice are euthanized on an individual basis when the s.c. tumor measured 18 mm in diameter or earlier if the mouse seemed moribund. The lungs are removed and weighed, and surface tumor colonies are quantified in a blinded fashion under a dissecting microscope. Experimental metastasis is evaluated by injecting 9×10⁴ viable tumor cells i.v. into the lateral tail vein of syngeneic female mice. All mice are euthanized on day 21 posttransplantation or earlier if the mice seemed moribund. The lungs are removed and weighed, and surface tumor colonies are quantified in a blinded fashion under a dissecting microscope. A 50% hydroxypropyl-β-cyclodextrin solution is prepared; at 20%, this solution serves as the vehicle. AMG487 is added to the 50% solution, and it is incubated in a sonicating water bath for 2 hours with occasional vortexing. Distilled water is added to give the appropriate final concentration of AMG487 in 20% of hydroxypropyl-β-cyclodextrin.

References:

- [1]. Johnson M, et al. Discovery and optimization of a series of quinazolinone-derived antagonists of CXCR3. *Bioorg Med Chem Lett*. 2007 Jun 15;17(12):3339-43.
- [2]. Walser TC, et al. Antagonism of CXCR3 inhibits lung metastasis in a murine model of metastatic breast cancer. *Cancer Res*. 2006 Aug 1;66(15):7701-7.
- [3]. Cambien B, et al. Organ-specific inhibition of metastatic colon carcinoma by CXCR3 antagonism. *Br J Cancer*. 2009 Jun 2;100(11):1755-64.
- [4]. Henne KR, et al. Sequential metabolism of AMG 487, a novel CXCR3 antagonist, results in formation of quinone reactive metabolites that covalently modify CYP3A4 Cys239 and cause time-dependent inhibition of the enzyme. *Drug Metab Dispos*. 2012 Jul;40(7):142

CAIndexNames:

Benzeneacetamide, N-[(1R)-1-[3-(4-ethoxyphenyl)-3,4-dihydro-4-oxopyrido[2,3-d]pyrimidin-2-yl]ethyl]-N-(3-pyridinylmethyl)-4-(trifluoromethoxy)-

SMILES:

O=C(N([C@@H](C1=NC2=NC=CC=C2C(N1C3=CC=C(OCC)C=C3)=O)C)CC4=CC=CN=C4)CC5=CC=C(OC(F)(F)F)C=C5

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

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