Binimetinib

Cat. No.: HY-15202

CAS No.: 606143-89-9

Molecular Formula: $C_{17}H_{15}BrF_2N_4O_3$

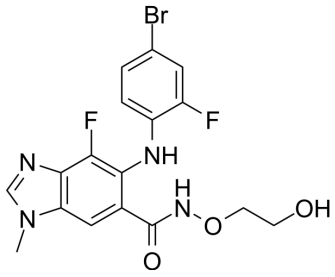
Molecular Weight: 441.23

Target: MEK; Autophagy

Pathway: MAPK/ERK Pathway; Autophagy

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	1 year
	-20°C	6 months



SOLVENT & SOLUBILITY

In Vitro

DMSO : 50 mg/mL (113.32 mM; Need ultrasonic)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.2664 mL	11.3320 mL	22.6639 mL
5 mM	0.4533 mL	2.2664 mL	4.5328 mL
10 mM	0.2266 mL	1.1332 mL	2.2664 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 1% CMC >> 0.5% Tween-80
   Solubility: 10 mg/mL (22.66 mM); Suspended solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (5.67 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (5.67 mM); Clear solution
4. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.67 mM); Clear solution
5. Add each solvent one by one: 5% DMSO >> 40% PEG300 >> 5% Tween-80 >> 50% saline
   Solubility: ≥ 2.5 mg/mL (5.67 mM); Clear solution
6. Add each solvent one by one: 5% DMSO >> 95% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (5.67 mM); Clear solution

BIOLOGICAL ACTIVITY

Description Binimetinib (MEK162) is an oral and selective MEK1/2 inhibitor. Binimetinib (MEK162) inhibits MEK with an IC_{50} of 12 nM.

IC_{50} & Target	MEK 12 nM (IC_{50})	Autophagy
In Vitro	In MCF7 cells, RSK3 or RSK4 expression decreases response to treatment with any of the PI3K inhibitors alone. However, the combination of PI3K inhibition with Binimetinib (MEK162) or BI-D1870 completely reverses the resistance of RSK-expressing cells[2]. Binimetinib (MEK162) blocks basal ERK phosphorylation in all HRAS mutant cell lines. The combination of RAD001 and AZD6244/MEK162 causes a stronger inhibition of S6 kinase than single use of RAD001 on Western blot. The combination of RAD001 and AZD6244/MEK162 also translated in a stronger blockade of cell growth in HRAS mutant cells than single use. Binimetinib (MEK162) shows stronger synergism with RAD001 than AZD6244[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.	
In Vivo	Treatment with Binimetinib (ARRY-438162) reduces disease severity in a dose-related manner in both animal models. ARRY-438162 in the CIA model inhibits increases in ankle diameter by 27% and 50% at 1 and 3 mg/kg, while Ibuprofen has 46% inhibition. When combined with Ibuprofen, these same two doses result in 74% and 72% inhibition, respectively. Microscopic examination of the ankle joints show Binimetinib (ARRY-438162) significantly inhibits lesions (inflammation, cartilage damage, pannus formation and bone resorption) by 32% and 60% at 1 and 3 mg/kg, while treatment with Ibuprofen alone results in 17% inhibition, which is not significantly different from the controls. When these two doses of Binimetinib (ARRY-438162) are combined with ibuprofen, the result is 54% and 77% inhibition of joint destruction. In AIA, 3 and 10 mg/kg of Binimetinib (ARRY-438162) inhibit AIA ankle diameter 11% and 34%, while MTX has 33% inhibition. When combined with MTX, 3 and 10 mg/kg of Binimetinib (ARRY-438162) result in 55% and 71% inhibition. Microscopic examination of ankle joints for inflammation and bone resorption also shows improved efficacy versus either compound alone[1]. When Binimetinib (MEK162) is combined with BEZ235, a significant reduction of tumor growth is observed (P=0.01). This increase in antitumor activity is accompanied by a decrease in phospho-ERK and phospho-S6 staining. No significant changes are observed in phospho-4EBP1 staining, a direct target of mTOR activity[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.	

PROTOCOL

Cell Assay [2]	MCF7 cells infected as indicated are seeded in 12-well plates (2×10^4). After 24 hours, cells are treated with BEZ235 (100 or 200 nM), BKM120 (0.75 or 1 μM), GDC-0941 (1 μM), or MK2206 (2 μM) alone or in combination with Binimetinib (MEK162) (1 μM), BI-D1870 (10 μM), or AZD6244 (1 μM), as indicated in text. Cell numbers are quantified by fixing cells with 4% glutaraldehyde or methanol, washing the cells twice in H_2O, and staining the cells with 0.1% crystal violet. The dye is subsequently extracted with 10% acetic acid, and its absorbance is determined (570 nm). Growth curves are performed in triplicate. Viability assays with CellTiter-Glo are performed by plating 2,000 cells in 96-well plates, adding the drug at 24 hours, and assaying 4 to 5 days after drug addition. Cell-cycle and hypodiploid apoptotic cells are quantified by flow cytometry. Briefly, cells are washed with PBS, fixed in cold 70% ethanol, and then stained with propidium iodide while being treated with RNase. Quantitative analysis of sub-G_1 cells is carried out in a FACScalibur cytometer using Cell Quest software [2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1][2]	Mice[2] Six-week-old female athymic nude Foxn1^{nu} mice are used. Mice are treated once daily with placebo, BEZ235, BKM120, MK-2206, or Binimetinib (MEK162) by oral gavage. BEZ235 (25-30 mg/kg, 6IW [6 days on 1 day off]) and BKM120 (30 mg/kg, 6IW) are dissolved in 10% NMP-90% PEG, freshly formulated, and administrated within 30 minutes. MK-2206 (100 mg/kg, 3IW) is formulated in 30% Captisol and Binimetinib (MEK162) (6 mg/kg, BID) in 0.5% Tween-80, 1% carboxymethyl cellulose. For tumor growth studies, mice are treated for 7-24 days, depending on the xenograft model and treatment regime. Tumor xenografts are measured with calipers 3 times a week, and tumor volume is determined using the following formula: (length×width^2)×(π/6). At the end of the experiment, the animals are anesthetized with 1.5% isofluorane-air mixture and killed by cervical dislocation. Tumors are removed 2 hours following the last administration. Rats[1] Rat collagen-induced arthritis (CIA) and rat adjuvant-induced arthritis (AIA) models are used to determine efficacy in the

subacute inflammation setting. In the CIA studies, rats with established disease, induced by injections of Type II collagen, are treated with 0.3, 1 or 3 mg/kg ARRY-438162 (PO, BID) with or without 30 mg/kg ibuprofen (PO, QD) for six days. Body weight and ankle diameter are used to monitor disease progression on days 0-7. The AIA model is induced by an injection of a lipoidal amine in FCA on day 0. The AIA rats are treated with 1, 3 or 10 mg/kg Binimetinib (ARRY-438162) (PO, QD) beginning on day 8 and continuing for 6 days, with or without the addition of 0.05 mg/kg CL14377 (PO, QD) which is dosed days 0-13. Disease progression is monitored on days 7-14 measuring both paw diameter and body weight.

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Cancer Cell. 2020 Mar 16;37(3):387-402.e7.
- Sci Transl Med. 2018 Jul 18;10(450):eaaq1093.
- Neuro Oncol. 2019 Mar 18;21(4):486-497.
- Adv Sci (Weinh). 2023 Nov 29:e2303088.
- Sci Adv. 2023 Jun 2;9(22):eadc9273.

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REFERENCES

[1]. J Pheneger, et al. 2006, ACR Annual Scientific Meeting. Abst 794.

[2]. Serra V, et al. RSK3/4 mediate resistance to PI3K pathway inhibitors in breast cancer. J Clin Invest, 2013, 123(6), 2551-2563.

[3]. Kiessling MK, et al. Mutant HRAS as novel target for MEK and mTOR inhibitors. Oncotarget. 2015 Dec 8;6(39):42183-96.

[4]. Cheng H, et al. PIK3CA(H1047R)- and Her2-initiated mammary tumors escape PI3K dependency by compensatory activation of MEK-ERK signaling. Oncogene. 2016 Jun 9;35(23):2961-70.

[5]. Seip K, et al. Fibroblast-induced switching to the mesenchymal-like phenotype and PI3K/mTOR signaling protects melanoma cells from BRAF inhibitors. Oncotarget. 2016 Apr 12;7(15):19997-20015.

Tel: 609-228-6898 Fax: 609-228-5909 E-mail: tech@MedChemExpress.com

Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA