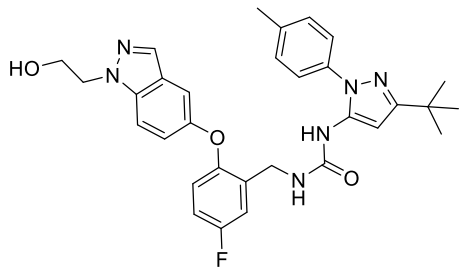
# Product data sheet

| | |
|---|---|
| MedKoo Cat#: 200294<br>Name: Pexmetinib<br>CAS#: 945614-12-0<br>Chemical Formula: $C_{31}H_{33}FN_6O_3$<br>Exact Mass: 556.25982<br>Molecular Weight: 556.63 |  |
| Product supplied as: | Powder |
| Purity (by HPLC): | ≥ 98% |
| Shipping conditions | Ambient temperature |
| Storage conditions: | Powder: -20°C 3 years; 4°C 2 years. |
| | In solvent: -80°C 3 months; -20°C 2 weeks. |

**1. Product description:**

Pexmetinib, also known as ARRY-614, is an orally bioavailable small-molecule inhibitor of p38 and Tie2 kinases with potential antineoplastic, anti-inflammatory and antiangiogenic activities. p38/Tie2 kinase inhibitor Arry-614 binds to and inhibits the activities of p38 and Tie2 kinases, which may inhibit the production of proinflammatory cytokines and may decrease tumor angiogenesis and tumor cell growth and survival. p38 is a MAP kinase that is often upregulated in cancer cells, playing a crucial part in the production of a variety of cytokines involved in inflammation and cellular proliferation such as tumor necrosis factor (TNF) and interleukin (IL)-1 and -6. Tie2 is an endothelial cell specific receptor that is activated by angiopoietins, growth factors required for angiogenesis.

**2. CoA, QC data, SDS, and handling instruction**

SDS and handling instruction, CoA with copies of QC data (NMR, HPLC and MS analytical spectra) can be downloaded from the product web page under "QC And Documents" section. Note: copies of analytical spectra may not be available if the product is being supplied by MedKoo partners. Whether the product was made by MedKoo or provided by its partners, the quality is 100% guaranteed.

**3. Solubility data**

| Solvent | Max Conc. mg/mL | Max Conc. mM |
|---|---|---|
| DMSO | 30.0 | 53.9 |

**4. Stock solution preparation table:**

| Concentration / Solvent Volume / Mass | 1 mg | 5 mg | 10 mg |
|---|---|---|---|
| 1 mM | 1.80 mL | 8.98 mL | 17.97 mL |
| 5 mM | 0.36 mL | 1.80 mL | 3.59 mL |
| 10 mM | 0.18 mL | 0.90 mL | 1.80 mL |
| 50 mM | 0.04 mL | 0.18 mL | 0.36 mL |

**5. Molarity Calculator, Reconstitution Calculator, Dilution Calculator**

Please refer the product web page under section of "Calculator"

**6. Recommended literature which reported protocols for in vitro and in vivo study**

In vitro study

1. Bachegowda L, Morrone K, Winski SL, Mantzaris I, Bartenstein M, Ramachandra N, Giricz O, Sukrithan V, Nwankwo G, Shahnaz S, Bhagat T, Bhattacharyya S, Assal A, Shastri A, Gordon-Mitchell S, Pellagatti A, Boultwood J, Schinke C, Yu Y, Guha C, Rizzi J, Garrus J, Brown S, Wollenberg L, Hogeland G, Wright D, Munson M, Rodriguez M, Gross S, Chantry D, Zou Y, Platanias L, Burgess LE, Pradhan K, Steidl U, Verma A. Pexmetinib: A Novel Dual Inhibitor of Tie2 and p38 MAPK with Efficacy in Preclinical Models of Myelodysplastic Syndromes and Acute Myeloid Leukemia. Cancer Res. 2016 Aug 15;76(16):4841-4849. doi: 10.1158/0008-5472.CAN-15-3062. Epub 2016 Jun 10. PMID: 27287719; PMCID: PMC5398415.

In vivo study

1. Bachegowda L, Morrone K, Winski SL, Mantzaris I, Bartenstein M, Ramachandra N, Giricz O, Sukrithan V, Nwankwo G, Shahnaz S, Bhagat T, Bhattacharyya S, Assal A, Shastri A, Gordon-Mitchell S, Pellagatti A, Boultwood J, Schinke C, Yu Y, Guha C, Rizzi J, Garrus J, Brown S, Wollenberg L, Hogeland G, Wright D, Munson M, Rodriguez M, Gross S, Chantry D, Zou Y, Platanias L, Burgess LE, Pradhan K, Steidl U, Verma A. Pexmetinib: A Novel Dual Inhibitor of Tie2 and p38 MAPK with Efficacy in Preclinical Models

of Myelodysplastic Syndromes and Acute Myeloid Leukemia. Cancer Res. 2016 Aug 15;76(16):4841-4849. doi: 10.1158/0008-5472.CAN-15-3062. Epub 2016 Jun 10. PMID: 27287719; PMCID: PMC5398415.

**7. Bioactivity**

Biological target:

Pexmetinib is a Tie-2 and p38 MAPK dual inhibitor, with IC50s of 1 nM, 35 nM and 26 nM for Tie-2, p38α and p38β, respectively.

In vitro activity

To determine the efficacy of pexmetinib in human hematopoietic cells, leukemic KG1 cells were treated with TNF-α with and without pexmetinib for indicated times and immunoblotted for phospho/activated p38 MAPK. TNF-α led to activation of p38 MAPK that was completely abrogated by pexmetinib treatment (Fig 6A). Downstream mediators of p38 MAPK, MAPKAPK2 and EIF4E were also evaluated by immunoblotting and pexmetinib was able to inhibit the activation of these effector kinases after TNF exposure. (Fig 6B,C). To assess the functional role of pexmetinib in human hematopoiesis, primary CD34+ stem cells were grown in methylcellulose media in the presence and absence of TNF-α (5ng/ml) and pexmetinib (0.1μM). Erythroid (BFU-E) and myeloid (CFU-GM) colonies were assessed after 14 days and revealed that TNF led myelosuppressive effects were significantly reversed by pexmetinib treatment (Fig 6D)(N=4, TTest, P Value<0.05). Finally, the effects of pexmetinib were assessed on leukemic cell proliferation and revealed the ability to significantly inhibit proliferation in vitro for two different AML derived cell lines (Fig 6E,F).

Reference: Cancer Res. 2016 Aug 15; 76(16): 4841–4849. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5398415/

In vivo activity

Due to similar protein binding between mouse and human plasma, this study was able to test this prediction by performing murine in vivo studies with HEK-Tie2 xenografts to assess the relationship between plasma concentration and target inhibition in lung (p-p38) or tumor (p-p38 and pTie-2). There was good concordance between plasma concentrations required to inhibit the p-p38 as assessed by immunoblot and the functional readout of LPS-induced TNFα, so data for this target were combined to generate an in vivo inhibitory value (Fig 5C). This study determined that murine plasma concentrations required to achieve 50% inhibition for pTie2 and p-p38 were 2066 nM and 203 nM, respectively, confirming that our predictions from protein binding-corrected in vitro inhibition were highly accurate.

Reference: Cancer Res. 2016 Aug 15; 76(16): 4841–4849. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5398415/

*Note: The information listed here was extracted from literature. MedKoo has not independently retested and confirmed the accuracy of these methods. Customer should use it just for a reference only.*