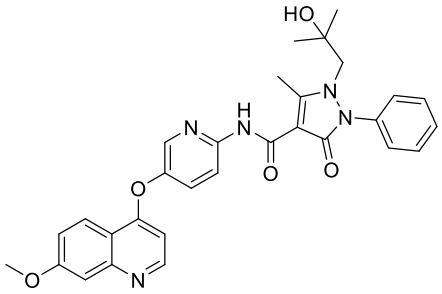
Product data sheet

MedKoo Cat#: 205898 Name: AMG-458 CAS#: 913376-83-7 Chemical Formula: $C_{30}H_{29}N_5O_5$ Exact Mass: 539.21687 Molecular Weight: 539.58176	
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:
AMG 458 is a potent c-Met inhibitor with Ki of 1 nM ~ 2.0 nM. AMG-458 was found to significantly inhibit tumor growth in the NIH3T3/TPR-Met and U-87 MG xenograft models with no adverse effect on body weight.

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	26.0	48.19

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	1 mg	5 mg	10 mg
1 mM	1.85 mL	9.27 mL	18.53 mL
5 mM	0.37 mL	1.85 mL	3.71 mL
10 mM	0.19 mL	0.93 mL	1.85 mL
50 mM	0.04 mL	0.19 mL	0.37 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. Teffera Y, Colletti AE, Harmange JC, Hollis LS, Albrecht BK, Boezio AA, Liu J, Zhao Z. Chemical reactivity of methoxy 4-o-aryl quinolines: identification of glutathione displacement products in vitro and in vivo. Chem Res Toxicol. 2008 Nov;21(11):2216-22. doi: 10.1021/tx800307n. PMID: 18837519.

In vivo study

1. Teffera Y, Colletti AE, Harmange JC, Hollis LS, Albrecht BK, Boezio AA, Liu J, Zhao Z. Chemical reactivity of methoxy 4-o-aryl quinolines: identification of glutathione displacement products in vitro and in vivo. Chem Res Toxicol. 2008 Nov;21(11):2216-22. doi: 10.1021/tx800307n. PMID: 18837519.
2. Liu L, Siegmund A, Xi N, Kaplan-Lefko P, Rex K, Chen A, Lin J, Moriguchi J, Berry L, Huang L, Teffera Y, Yang Y, Zhang Y, Bellon SF, Lee M, Shimanovich R, Bak A, Dominguez C, Norman MH, Harmange JC, Dussault I, Kim TS. Discovery of a potent, selective, and orally bioavailable c-Met inhibitor: 1-(2-hydroxy-2-methylpropyl)-N-(5-(7-methoxyquinolin-4-yloxy)pyridin-2-yl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide (AMG 458). J Med Chem. 2008 Jul 10;51(13):3688-91. doi: 10.1021/jm800401t. Epub 2008 Jun 14. PMID: 18553959.

7. Bioactivity
Biological target:

AMG 458 is a potent c-Met inhibitor with Ki of 1.2 nM, ~350-fold selectivity for c-Met than VEGFR2 in cells.

Product data sheet

In vitro activity

When incubated with rat or human liver microsomes, AMG 458 exhibited covalent binding to proteins (Figure 2). The binding was NADPH-independent, indicating that metabolic activation was not taking place. The addition of GSH to the incubation medium did not cause a significant reduction in bound radioactivity. The binding was not reduced significantly when the enzyme was inactivated by heating, suggesting that the mechanism was not enzyme-dependent. To understand the nature of this covalent binding, we set out to determine the structure of the thioether adduct(s) formed.

Reference: Chem Res Toxicol. 2008 Nov;21(11):2216-22. https://pubmed.ncbi.nlm.nih.gov/18837519/

In vivo activity

As a potent inhibitor of mouse c-Met (Ki = 2.0, IC50(CT26) = 120 nM; Table 2), 17 (AMG-458) was evaluated in the mouse liver pharmacodynamic assay. Oral dosing of 17 inhibited HGF-mediated c-Met phosphorylation in a dose-dependent manner with an approximate ED90 of 30 mg/kg and an associated plasma exposure of approximately 15 μM at 6 h (Figure 2A). There was a clear correlation between the inhibition of liver c-Met phosphorylation and the plasma concentration of 17.

Reference: J Med Chem. 2008 Jul 10;51(13):3688-91. https://pubmed.ncbi.nlm.nih.gov/18553959/