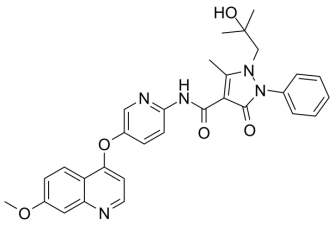
AMG-458

Cat. No.:	HY-14723
CAS No.:	913376-83-7
Molecular Formula:	$C_{30}H_{29}N_5O_5$
Molecular Weight:	539.58
Target:	c-Met/HGFR
Pathway:	Protein Tyrosine Kinase/RTK
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 6 months -20°C 1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : 50 mg/mL (92.66 mM; ultrasonic and warming and heat to 60°C)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.8533 mL	9.2665 mL	18.5329 mL
5 mM	0.3707 mL	1.8533 mL	3.7066 mL
10 mM	0.1853 mL	0.9266 mL	1.8533 mL

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

BIOLOGICAL ACTIVITY

Description

AMG-458 is a potent, selective and orally bioavailable c-Met inhibitor, with K_i values of 1.2 nM and 2.0 nM for human and mouse c-Met, respectively[1].

IC_{50} & Target

human c-Met 1.2 nM (Ki)	mouse c-Met 2.0 nM (Ki)	V1092I 1.1 nM (Ki)	D1228H 2.2 nM (Ki)
M1250T 4.1 nM (Ki)	H1094R 0.5 nM (Ki)	Y1230H 4.5 nM (Ki)	VEGDR2 4100 nM (Ki)

In Vivo

AMG-458 (orally, 30, 100 mg/kg) significantly inhibits tumor growth in the NIH3T3/TPR-Met and U-87 MG xenograft models with no adverse effect on body weight[1].

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

Animal Model:	NIH-3T3/TPR-Met model and U-87 MG human glioblastoma xenograft model[1].

Dosage:	10, 30, 100 mg/kg.
Administration:	Orally q.d. or b.i.d.
Result:	With an ED_{50} of 12 mg/kg and an ED_{90} of 34 mg/kg in NIH-3T3/TPR-Met model. With an ED_{50} of 16 mg/kg and an ED_{90} of 59 mg/kg in U-87 MG human glioblastoma xenograft model. Significantly inhibited tumor growth at 30 and 100 mg/kg q.d. and 30 mg/kg b.i.d. without adverse effect on body weight.

Animal Model:	Balb/c mouse and SD rat[1].
Dosage:	1 mg/kg (Pharmacokinetic Analysis).
Administration:	IV dose: 1 mg/kg (20% Captisol with pH adjusted to 3.5 using methanesulfonic acid).
Result:	Exhibited CL ((L/h)/kg) values of 0.16 and 0.73, V_{ss} (L/kg) values of 0.31 and 0.62, $t_{1/2}$ (h) values of 1.3 and 1.0 in mouse and rat, respectively.

REFERENCES

[1]. Longbin Liu, et al. 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.

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