AG-490

Cat. No.: HY-12000

CAS No.: 133550-30-8

Molecular Formula: $C_{17}H_{14}N_2O_3$

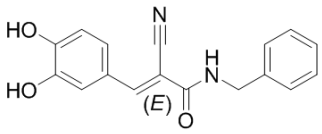
Molecular Weight: 294.3

Target: EGFR; STAT; Autophagy

Pathway: JAK/STAT Signaling; Protein Tyrosine Kinase/RTK; Stem Cell/Wnt; Autophagy

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 (169.89 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	3.3979 mL	16.9895 mL	33.9789 mL
5 mM	0.6796 mL	3.3979 mL	6.7958 mL
10 mM	0.3398 mL	1.6989 mL	3.3979 mL

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

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (8.49 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (8.49 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

AG-490 is a tyrosine kinase inhibitor that inhibits EGFR, Stat-3 and JAK2/3.

IC_{50} & Target

EGFR and Stat-3[1]

In Vitro

AG490 inhibits the activation of Stat-3 by selectively blocking JAK2. AG490 is used to selectively inhibit JAK/Stat-3 activation. At a dose of 10 μM, Stat-3 phosphorylation is decreased by >95% and cell viability is maintained. AG490 at a dose of 10 μM results in >95% decrease in pStat-3 in EGF-stimulated A431 cells with no effect on Stat-3 mass[1]. AG-490 is a potent inhibitor of the JAK3/STAT, JAK3/AP-1, and JAK3/MAPK pathways and their cellular consequences. AG-490 abolishes IL-2-inducible [^{3}H]thymidine incorporation in a dose-dependent manner, displaying an IC_{50} of 25 μM. AG-490 potently inhibits IL-2-mediated

	proliferation in T cells, results distinct from previous studies that showed this agent induced apoptosis in ALL cells while exerting apparently no effects on the growth of mitogen-stimulated normal T cells[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	AG490 significantly inhibits the development of type 1 diabetes (T1D) ($p = 0.02$, $p = 0.005$; at two different time points). Monotherapy of newly diagnosed diabetic NOD mice with AG490 (1 mg/mouse) markedly results in disease remission in treated animals (n=23) in comparision to the absolute inability (0%; 0/10, p=0.003, Log-rank test) of DMSO and sustained eugluycemia is maintained for several months following drug withdrawal[3]. AG490 (1-10 μg) significantly attenuates λ-carrageenan-induced thermal hyperalgesia in a dose-dependent manner. AG490 also reduces mechanical hyperalgesia[4]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	A colorimetric cell proliferation assay is performed using the CellTiter 96 kit. Briefly, A431 cells are plated in 96-well plates (2000 cells/well) and cultured in DMEM/HAM's F-12 supplemented with 10% FCS for 24 h. Cells are incubated in serum-free media for 24 h. EGF (10 ng/mL) is added to all wells. Tyrphostin AG1478 (0.25 mM) and AG490 (10 mM) are added alone or in combination and the culture is incubated for the appropriate time. Medium is aspirated and CellTiter 96 Aqueous One Solution Reagent (20 μL) is added to each well. The plates are incubated at 37°C for up to 1 h and absorbance recorded at 490 nm using a 96-well plate reader. Data are derived from at least three independent experiments (in triplicate) for the both single agents and combination studies. IC_{50} values for Tyrphostin AG1478 (EGFR inhibitor) and AG490 (JAK/STAT inhibitor) are determined. The growth inhibitory effects of the combination are quantified using the Calucsyn software program[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [3][4]	Mice[3] Female NOD/LtJ, NOD.Scid, and BALB/c mice are used. One vial of compound containing 5 mg of AG490 is injected into5 mice (1 mg/mouse) via the i.p route. The control groups are receive the same volume of the vehicle under the same regimens and conditions. Rats[4] A total of 28 Male Sprague-Dawley rats (250-300 g) are used. The experiments are performed in rats 48 h after λ-carrageenan injection. A total of 4 groups (n=6) of rats are randomly included in the dose-response study. Group 1 is the vehicle control, which receive 100 μL i.pl. injection of 3.5% DMSO in saline. Groups 2-4 are injected with 3 different doses of AG490 (1, 5 or 10 μg). To study the effects of naloxone on AG490-induced antinociception, an additional group of rats (group 5; n=4) is observed. Group 5 is co-administered with AG490 (10 μg) and Naloxone (10 μg). The drugs are administered i.pl. in a volume of 100 μl. As reported earlier, the in vivo pharmacological effects of AG490 are observed 4 h after treatment. Thus, the behavioral tests are performed before (baseline assessment) and 4 h after treatment. First, the rats are subjected to the thermal hyperalgesia test; 10 min later, the paw pressure test is performed on the same set of rats. All the experiments are performed between 8:00 a.m. and 2:00 p.m. to reduce the confounding influence of diurnal variations, and all the procedures are performed in a blinded fashion. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Oncogene. 2017 May 25;36(21):2946-2956.
- J Exp Clin Cancer Res. 2019 Aug 22;38(1):370.
- Brain Behav Immun. 2019 Aug;80:711-724.
- Cell Death Dis. 2019 Jun 13;10(6):465.
- Cell Death Dis. 2019 Apr 30;10(5):353.

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REFERENCES

[1]. Dowlati A, et al. Combined inhibition of epidermal growth factor receptor and JAK/STAT pathways results in greater growth inhibition in vitro than single agent therapy. Mol Cancer Ther. 2004 Apr;3(4):459-63

[2]. Wang LH, et al. JAK3, STAT, and MAPK signaling pathways as novel molecular targets for the tyrphostin AG-490 regulation ofIL-2-mediated T cell response. J Immunol. 1999 Apr 1;162(7):3897-904.

[3]. Davoodi-Semiromi A, et al. The tyrphostin agent AG490 prevents and reverses type 1 diabetes in NOD mice. PLoS One. 2012;7(5):e36079.

[4]. Cheppudira BP, et al. Anti-hyperalgesic effects of AG490, a Janus kinase inhibitor, in a rat model of inflammatory pain. Biomed Rep. 2015 Sep;3(5):703-706.

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