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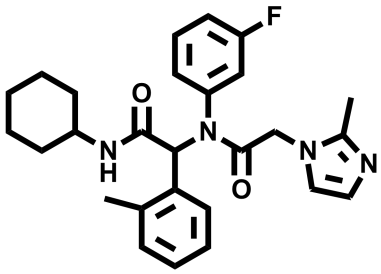
AGI-5198 (IDH-C35) --- Mutant IDH1 Inhibitor

Chemical Name: N-cyclohexyl-2-(N-(3-fluorophenyl)-2-(2-methyl-1H-imidazol-1-yl)acetamido)-2-(o-tolyl)acetamide



Molecular Weight:	462.56
Formula:	$C_{27}H_{31}FN_4O_2$
Purity:	≥98%
CAS#:	1355326-35-0
Solubility:	DMSO up to 100mM
Storage	Powder: 4°C 1 year DMSO: 4°C 3 month -20°C 1 year

Biological Activity:

AGI-5198 (IDH-C35) is the first highly potent and selective mutant IDH1 inhibitor that was shown to have anti-tumor efficacy and lower tumor 2‑HG (2-hydroxyglutarate) in vivo. It inhibits IDH1 R132H mutant and R132C mutant in vitro with IC_{50} ~0.07 μM and ~0.16 μM, respectively, but not wild-type IDH1 or any of the examined IDH2 isoforms (IC_{50} > 100 μM). AGI-5198 has good cellular activities in TS603 glioma cell line, also inhibits 2-HG production in HT1080 and U87MG cells with IC_{50} ~0.48 μM and IC_{50} ~0.07 μM, respectively. In R132H-IDH1 glioma xenografts (TS603), AGI-5198 (450 mg/kg) caused 50-60% growth inhibition with no signs of toxicity during three weeks of daily treatment, but it did not affect the growth of IDH1 wild-type glioma xenografts (TS516). Under conditions of near complete R-2HG (R-2-hydroxyglutarate) inhibition, AGI-5198 induced demethylation of histone H3K9me3 and expression of genes associated with gliogenic differentiation. Blockade of mutant IDH1 impaired the growth of IDH1-mutant—but not IDH1-wild-type—glioma cells without appreciable changes in genome-wide DNA methylation. AGI-5198 could serve as a very useful chemical probe to assess the biological consequences of IDH1 mutations and the potential of IDH1 inhibitor for treating IDH1 mutant tumors.

How to Use:

In vitro: AGI-5198 was suggested to be used at 1.5-10μM final concentration in vitro.

In vivo: AGI-5198 could be orally dosed to mice at 150-450 mg/kg once per day for up to 3 weeks in glioma xenografts. It could be intraperitoneally (IP) dosed to mice at 50-150 mg/kg once or twice per day (formulation: 0.5% MC and 0.2% Tween 80) in the other animal studies.

Reference:

1. Dan Rohle, et al. An Inhibitor of Mutant IDH1 Delays Growth and Promotes Differentiation of Glioma Cells. (2013) Science. 340(6132):626-30.
2. Janeta Popovici-Muller, et al. Discovery of the First Potent Inhibitors of Mutant IDH1 That Lower Tumor 2-HG in Vivo. (2012) ACS Med. Chem. Lett. 3 (10), pp 850–855
3. Lenny Dang, et al. Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. (2009) Nature 462, 739-744.
4. Turcan S, et al. IDH1 mutation is sufficient to establish the glioma hypermethylator phenotype. (2012) Nature. 483(7390):479-83.