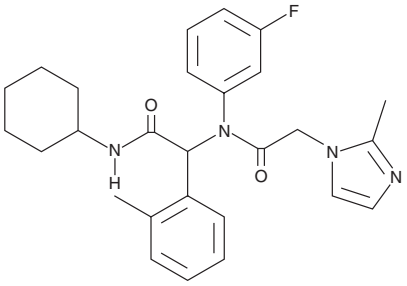
PRODUCT INFORMATION

AGI-5198

Item No. 14624

CAS Registry No.:	1355326-35-0
Formal Name:	N-[2-(cyclohexylamino)-1-(2-methylphenyl)-2-oxoethyl]-N-(3-fluorophenyl)-2-methyl-1H-imidazole-1-acetamide
MF:	$C_{27}H_{31}FN_4O_2$
FW:	462.6
Purity:	≥98%
Supplied as:	A crystalline solid
Storage:	-20°C
Stability:	≥4 years



Information represents the product specifications. Batch specific analytical results are provided on each certificate of analysis.

Laboratory Procedures

AGI-5198 is supplied as a crystalline solid. A stock solution may be made by dissolving the AGI-5198 in the solvent of choice, which should be purged with an inert gas. AGI-5198 is soluble in organic solvents such as ethanol, DMSO, and dimethyl formamide (DMF). The solubility of AGI-5198 in these solvents is approximately 5, 10, and 20 mg/ml, respectively.

AGI-5198 is sparingly soluble in aqueous buffers. For maximum solubility in aqueous buffers, AGI-5198 should first be dissolved in DMF and then diluted with the aqueous buffer of choice. AGI-5198 has a solubility of approximately 0.09 mg/ml in a 1:10 solution of DMF:PBS (pH 7.2) using this method. We do not recommend storing the aqueous solution for more than one day.

Description

Isocitrate dehydrogenases (IDHs) are nicotinamide adenine dinucleotide (NAD^+) and NAD phosphate ($NADP^+$)-dependent enzymes in the tricarboxylic acid cycle that catalyze oxidative decarboxylation of isocitrate producing a-ketoglutarate (2-OG) and carbon dioxide. IDH1 and IDH2 are mutated in >70% of lower grade gliomas.[1] The most common mutations map to arginine residues in the catalytic pockets of IDH1 (R132) or IDH2 (R140 and R172) and impart new gain of function catalytic activity leading to the NADPH-dependent conversion of 2-OG to 2-hydroxyglutarate (2-HG).[2-4] AGI-5198 is a potent, selective inhibitor of IDH1 R132H and R132C mutants *in vitro* with IC_{50} values of 0.07 and 0.16 µM, respectively, but not wild-type IDH1, wild-type IDH2, or IDH2 mutants (IC_{50}s > 100 µM).[5] AGI-5198 has been shown to have anti-tumor efficacy in the TS603 glioma cell line and to lower tumor 2-HG production in HT1080 and U87MG cells with IC_{50} values of 0.48 and 0.07 µM, respectively.[6] In R132H-IDH1 glioma xenografts, AGI-5198 (450 mg/kg/day) caused 50-60% growth inhibition over a treatment period of three weeks with no affect in the growth of IDH1 wild-type glioma xenografts.[5] Under conditions of near complete 2-HG inhibition, AGI-5198 can induce demethylation of histone H3K9me3 and expression of genes associated with gliogenic differentiation.[5]

References

1. Turcan, S., Rohle, D., Goenka, A., *et al. Nature* **483(7390)**, 479-483 (2012).
2. Reitman, Z.J. and Yan, H. *J. Natl. Cancer Inst.* **102(13)**, 932-941 (2010).
3. Dang, L., White, D.W., Gross, S., *et al. Nature* **462(7274)**, 739-744 (2009).
4. Koivunen, P., Lee, S., Duncan, C.G., *et al. Nature* **483(7390)**, 484-488 (2012).
5. Rohle, D., Popovici-Muller, J., Palaskas, N., *et al. Science* **340(6132)**, 626-630 (2013).
6. Popovici-Muller, J., Saunders, J.O., Salituro, F.G., *et al. ACS Med. Chem. Lett.* **3(10)**, 850-855 (2012).

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