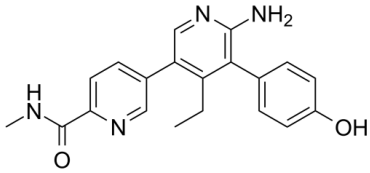
Data Sheet

Product Name:	GNE-6776
Cat. No.:	CS-0031103
CAS No.:	2009273-71-4
Molecular Formula:	C20H20N4O2
Molecular Weight:	348.40
Target:	Deubiquitinase
Pathway:	Cell Cycle/DNA Damage
Solubility:	DMSO : ≥ 100 mg/mL (287.03 mM)



BIOLOGICAL ACTIVITY:

GNE-6776 is a selective **USP7** inhibitor. IC50 & Target: USP7[1] **In Vitro:** GNE-6776 non-covalently targets USP7 12 Å distant from the catalytic cysteine. GNE-6776 attenuates ubiquitin binding and thus inhibits USP7 deubiquitinase activity. GNE-6776 interacts with acidic residues that mediate hydrogen-bond interactions with the ubiquitin Lys48 side chain. GNE-6776 targets cellular USP7, MDM2, and p53 signalling pathways.GNE-6776 selectively inhibits recombinant USP7 relative to 36 other deubiquitinases. GNE-6776 remains selective even at 100 μM, a more than sixfold higher concentration than used in cellular assays. GNE-6776 significantly inhibits USP7 while remaining selective against 44-47 other detected deubiquitinases[1]. **In Vivo:** Although efficacious exposure is only transiently achieved, GNE-6776 causes modest, although significant, EOL-1 xenograft growth delay[1].

PROTOCOL (Extracted from published papers and Only for reference)

Cell Assay: [1]**EOL-1 cells** are seeded into 384-well plates 24 h before compound addition. Cells are then incubated with compound (e.g., **GNE-6776; 0.003, 0.009, 0.027, 0.082, 0.25, 0.74, 2.22, 6.67, and 20 μM**) for 72 h or 120 h before assaying viability. Assays are performed in biological triplicate. Cells are incubated (37°C, 5% CO_2) in RPMI-1640, 2.5% FBS (72 h assay) or 5% FBS (120 h assay), and 2 mM glutamine throughout the assay. The reported IC_{50} and mean viability metrics are as follows: IC_{50} is the dose at which the estimated inhibition is 50% relative to untreated wells (that is, absolute IC_{50}). The mean viability is calculated[1].
Animal Administration: GNE-6776 is formulated as a suspension in 0.5% methylcellulose/0.2% Tween-80[1].[1]Mice[1]
GNE-6776 is administered at **200 mg/kg** (body weight) by **oral gavage** to **female C.B-17 SCID mice**, aged 12-16 weeks (n=3 per time point). No randomization is used for DMPK studies. At 0.5, 1, 2, 4, 8 and 24 h post-dose, blood samples are collected by terminal cardiac puncture into anticoagulant tubes (EDTA). Clarified plasma is then transferred to a fresh tube and snap frozen. GNE-6776 plasma concentrations are determined by LC-MS/MS[1].

References:

[1]. Kategaya L, et al. USP7 small-molecule inhibitors interfere with ubiquitin binding. Nature. 2017 Oct 26;550(7677):534-538.

CAIndexNames:

[3,3'-Bipyridine]-6-carboxamide, 6'-amino-4'-ethyl-5'-(4-hydroxyphenyl)-N-methyl-

SMILES:

CCC(C(C1=CC=C(O)C=C1)=C(N)N=C2)=C2C3=CC=C(C(NC)=O)N=C3

Caution: Product has not been fully validated for medical applications. For research use only.

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