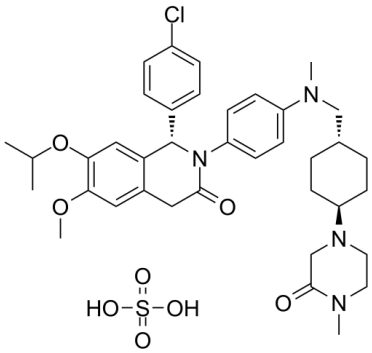
Data Sheet

Product Name:	NVP-CGM097 (sulfate)
Cat. No.:	CS-6873
CAS No.:	1313367-56-4
Molecular Formula:	C38H49ClN4O8S
Molecular Weight:	757.34
Target:	E1/E2/E3 Enzyme; MDM-2/p53
Pathway:	Apoptosis; Metabolic Enzyme/Protease
Solubility:	H2O : ≥ 140 mg/mL (184.86 mM)



BIOLOGICAL ACTIVITY:

NVP-CGM097 sulfate is a potent and selective **MDM2** inhibitor with **IC_{50}** of 1.7±0.1 nM for **hMDM2**. IC50 & Target: IC50 & Target: IC50: 1.7±0.1 nM (hMDM2)[1] **In Vitro:** NVP-CGM097 binds to human MDM2 with an IC_{50} of 1.7 nM and shows high selectivity over MDM4 (IC_{50}=2000 nM). NVP-CGM097 is about four times more potent than Nutlin-3a (IC_{50}=8 nM). In addition, NVP-CGM097 shows no significant activity against Bcl-2:Bak, Bcl-2:Bad, Mcl-1:Bak, Mcl-1:NOXA, XIAP:BIR3, and c-IAP:BIR3 protein-protein interactions. NVP-CGM097 significantly inhibits the proliferation of cells expressing wild-type p53, while sparing the p53 null cells with a 35-58-fold difference. NVP-CGM097 is able to significantly redistribute wild-type p53 into the cell nucleus with an IC_{50} of 0.224 μM, demonstrating its ability to inhibit the p53:MDM2 interaction in living cells. NVP-CGM097 significantly inhibits the proliferation of cells expressing wild-type p53, while sparing the p53 null cells with a 35-58-fold difference. NVP-CGM097 inhibtis HCT116 ($p53^{WT/WT}$) with IC_{50} of 454±136 nM[1]. **In Vivo:** NVP-CGM097 is able to inhibit the interaction between p53 and MDM2 and reactivate the p53 pathway in a MDM2-amplified SJSA-1 human tumor model, as judged by elevation of p21 mRNA levels, a pharmacodynamic (PD) indicator for p53 activity. p21 mRNA levels are found to increase concomitantly with levels of NVP-CGM097 in tumor-bearing rats dosed at 30 mg/kg. The PD response is biphasic and prolonged up to 24 h. Additional p53 target genes such as MDM2 and PUMA mRNA levels are assessed in the tumor samples as well and showed a similar behavior. Daily treatment with NVP-CGM097 dose dependently and significantly inhibits SJSA-1 tumor growth in rats. It promotes stable disease at 20 mg/kg, which is associated with a plasma AUC_{0-24} of 163 μM•h. After iv administration, the total blood clearance (CL) of NVP-CGM097 is 5 mL/min per kg for mouse, 7 mL/min per kg for rat, 3 mL/min per kg for dog, and 4 mL/min per kg for monkey. The apparent terminal half-life ($t_{1/2}$) is long in rodents and monkey (6-12 h) but is comparatively longer in dogs (20 h). After oral dosing, NVP-CGM097 is well absorbed with T_{max} occurring between 1 and 4.5 h in all species tested[1].

PROTOCOL (Extracted from published papers and Only for reference)

Cell Assay: NVP-CGM097 is prepared in DMSO and stored, and then diluted with appropriate medium before use[1].[1]Two pairs of cell lines are used to assess NVP-CGM097 p53-dependent antiproliferative effects: (1) an isogenic pair of HCT116 cell lines either expressing wild-type p53 or knocked-out for the p53 gene and (2) a nonisogenic pair of osteosarcoma cell lines either endogenously expressing wild-type p53 and amplified for MDM2 (SJSA-1 cells) or null for p53 (SAOS-2 cells)[1]. **Animal Administration:** NVP-CGM097 is prepared in DMSO and diluted with saline or PBS[1].[1]Female athymic rats bearing subcutaneous xenotransplants of SJSA-1 tumors (n=5-12) are treated at 5, 10, 20, or 30 mg/kg or three times a week on Monday, Wednesday, and Friday (3qw M, W, F) at 30 or 70 mg/kg po for 14 days. Plasma AUCs are determined at the end of the study. Positive numbers indicate the percentage of tumor growth inhibition (T/C); negative numbers indicate the percentage of tumor regression[1].

References:

[1]. Holzer P, et al. Discovery of a Dihydroisoquinolinone Derivative (NVP-CGM097): A Highly Potent and Selective MDM2 Inhibitor Undergoing Phase 1 Clinical Trials in p53wt Tumors. J Med Chem. 2015 Aug 27;58(16):6348-58.

CAIndexNames:

3(2H)-Isoquinolinone, 1-(4-chlorophenyl)-1,4-dihydro-6-methoxy-7-(1-methylethoxy)-2-[4-[methyl[[trans-4-(4-methyl-3-oxo-1-piperazinyl)cyclohexyl]methyl]amino]phenyl]-, (1S)-, sulfate (1:1)

SMILES:

ClC(C=C1)=CC=C1[C@@H](C2=CC(OC(C)C)=C(OC)C=C2C3)N(C4=CC=C(N(C[C@@H]5CC[C@@H](N6CC(N(C)CC6)=O)CC5)C)C=C4)C3=O.O=S(O)(O)=O

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