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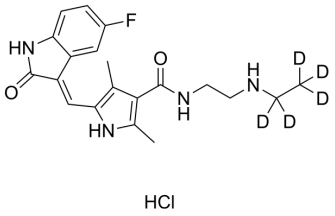
N-Desethyl Sunitinib-d_5 hydrochloride

Cat. No.:	HY-10873S2
CAS No.:	1261432-14-7
Molecular Formula:	$C_{20}H_{19}D_5ClFN_4O_2$
Molecular Weight:	411.91
Target:	Drug Metabolite; Isotope-Labeled Compounds
Pathway:	Metabolic Enzyme/Protease; Others
Storage:	Please store the product under the recommended conditions in the Certificate of Analysis.



HCl

BIOLOGICAL ACTIVITY

Description	N-Desethyl Sunitinib-d5 (hydrochloride) is a deuterated labeled N-Desethyl Sunitinib[1]. N-Desethyl Sunitinib (SU-12662) is a metabolite of sunitinib. Sunitinib is a potent, ATP-competitive VEGFR, PDGFRβ and KIT inhibitor with K_i values of 2, 9, 17, 8 and 4 nM for VEGFR -1, -2, -3, PDGFRβ and KIT, respectively[2].
In Vitro	Stable heavy isotopes of hydrogen, carbon, and other elements have been incorporated into drug molecules, largely as tracers for quantitation during the drug development process. Deuteration has gained attention because of its potential to affect the pharmacokinetic and metabolic profiles of drugs[1]. Sunitinib also potently inhibits Kit and FLT-3[2]. Sunitinib is a potent ATP-competitive inhibitor of VEGFR2 (Flk1) and PDGFRβ with K_i of 9 nM and 8 nM, respectively, displaying >10-fold higher selectivity for VEGFR2 and PDGFR than FGFR-1, EGFR, Cdk2, Met, IGFR-1, Abl, and src. In serum-starved NIH-3T3 cells expressing VEGFR2 or PDGFRβ, Sunitinib inhibits VEGF-dependent VEGFR2 phosphorylation and PDGF-dependent PDGFRβ phosphorylation with IC_{50} of 10 nM and 10 nM, respectively. Sunitinib inhibits VEGF-induced proliferation of serum-starved HUVECs with IC_{50} of 40 nM, and inhibits PDGF-induced proliferation of NIH-3T3 cells overexpressing PDGFRβ or PDGFRα with IC_{50} of 39 nM and 69 nM, respectively[3]. Sunitinib inhibits phosphorylation of wild-type FLT3, FLT3-ITD, and FLT3-Asp835 with IC_{50} of 250 nM, 50 nM, and 30 nM, respectively. Sunitinib inhibits the proliferation of MV4;11 and OC1-AML5 cells with IC_{50} of 8 nM and 14 nM, respectively, and induces apoptosis in a dose-dependent manner[4]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Sunitinib (20-80 mg/kg/day) exhibits broad and potent dose-dependent anti-tumor activity against a variety of tumor xenograft models including HT-29, A431, Colo205, H-460, SF763T, C6, A375, or MDA-MB-435, consistent with the substantial and selective inhibition of VEGFR2 or PDGFR phosphorylation and signaling in vivo. Sunitinib (80 mg/kg/day) for 21 days leads to complete tumor regression in six of eight mice, without tumor re-growing during a 110-day observation period after the end of treatment. Second round of treatment with Sunitinib remains efficacious against tumors that are not fully regressed during the first round of treatment. Sunitinib treatment results in significant decrease in tumor MVD, with appr 40% reduction in SF763T glioma tumors. SU11248 treatment results in a complete inhibition of additional tumor growth of luciferase-expressing PC-3M xenografts, despite no reduction in tumor size[3].?Sunitinib treatment (20 mg/kg/day) dramatically suppresses the growth subcutaneous MV4;11 (FLT3-ITD) xenografts and prolongs survival in the FLT3-ITD bone marrow engraftment model[4]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Mendel DB, et al. In vivo antitumor activity of SU11248, a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor and platelet-derived growth factor receptors: determination of a pharmacokinetic/pharmacodynamic relationship. Clin Can

[2]. O'Farrell AM, et al. SU11248 is a novel FLT3 tyrosine kinase inhibitor with potent activity in vitro and in vivo. Blood. 2003 May 1;101(9):3597-605. Epub 2003 Jan 16.

[3]. Sun L, et al. Discovery of 5-[5-fluoro-2-oxo-1,2- dihydroindol-(3Z)-ylidenemethyl]-2,4- dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylaminoethyl)amide, a novel tyrosine kinase inhibitor targeting vascular endothelial and platelet-derived growth factor r

[4]. Russak EM, et al. Impact of Deuterium Substitution on the Pharmacokinetics of Pharmaceuticals. Ann Pharmacother. 2019 Feb;53(2):211-216.

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