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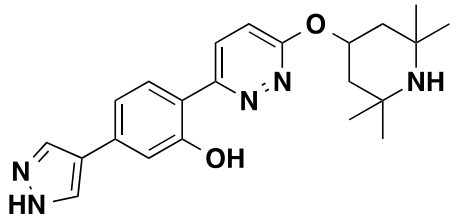
SMN2 Splicing Modulator – NVS-SM1

Chemical Name: 5-(1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)phenol



Molecular Weight:	393.49
Formula:	$C_{22}H_{27}N_5O_2$
Purity:	≥98%
CAS#:	n/a
Solubility:	DMSO up to 100 mM
Storage	Powder: 4°C 1 year DMSO: 4°C 3 month -20°C 1 year

Biological Activity:

NVS-SM1 is a highly potent, selective and orally active small molecule SMN2 splicing modulator enhancing SMN exon 7 inclusion with EC_{50} ~20 nM. It elevates full-length SMN protein and extends survival in a severe Spinal Muscular Atrophy (SMA) mouse model. The molecular mechanism of action for NVS-SM1 is via stabilization of the transient double-strand RNA structure formed by the SMN2 pre-mRNA and U1 small nuclear ribonucleic protein (snRNP) complex. The binding affinity of U1 snRNP to the 5' splice site is increased in a sequence-selective manner, discrete from constitutive recognition. This new mechanism demonstrates the feasibility of small molecule-mediated, sequence-selective splice modulation and the potential for leveraging this strategy in other splicing diseases. Currently NVS-SM1 is in phase I clinical trial for treatment of type I SMA.

How to Use:

In vitro: NVS-SM1 was used at 0.1-1 μM final concentration in vitro and in cellular assays.

In vivo: NVS-SM1 was dose to C/+ SMA mouse model by oral administration at 1-3 mg/kg once per day.

Reference:

1. Palacino J, et al. SMN2 splice modulators enhance U1-pre-mRNA association and rescue SMA mice. (2015) Nat Chem Biol. 11(7):511-7.