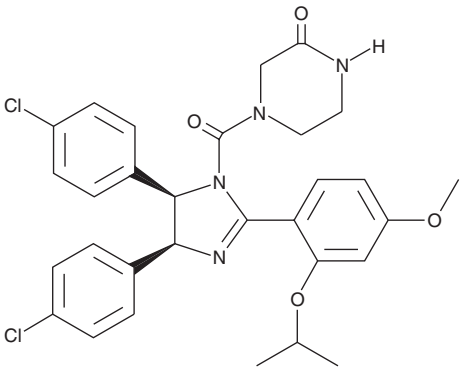
PRODUCT INFORMATION

(–)-Nutlin-3

Item No. 18585



CAS Registry No.:	675576-98-4
Formal Name:	4-[[(4S,5R)-4,5-*bis*(4-chlorophenyl)-4,5-dihydro-2-[4-methoxy-2-(1-methylethoxy)phenyl]-1H-imidazol-1-yl]carbonyl]-2-piperazinone
Synonym:	Nutlin 3a
MF:	$C_{30}H_{30}Cl_2N_4O_4$
FW:	581.5
Purity:	≥98%
Supplied as:	A crystalline solid
Storage:	-20°C
Stability:	≥2 years

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

Laboratory Procedures

(–)-Nutlin-3 is supplied as a crystalline solid. A stock solution may be made by dissolving the (–)-nutlin-3 in the solvent of choice. (–)-Nutlin-3 is soluble in dimethyl formamide (DMF), which should be purged with an inert gas. The solubility of (–)-nutlin-3 in these solvents is approximately 50 mg/ml.

(–)-Nutlin-3 is sparingly soluble in aqueous buffers. For maximum solubility in aqueous buffers, (–)-nutlin-3 should first be dissolved in DMF and then diluted with the aqueous buffer of choice. (–)-Nutlin-3 has a solubility of approximately 0.1 mg/ml in a 1:1 solution of DMF:PBS (pH 7.2) using this method. We do not recommend storing the aqueous solution for more than one day.

Description

The protein p53, often called the 'guardian of the genome,' is a transcription factor that is activated in response to cellular stress (low oxygen levels, heat shock, DNA damage, etc.) and acts to prevent further proliferation of the stressed cell by promoting cell cycle arrest or apoptosis.[1,2] Its role as a tumor suppressor is evident by the observation that approximately 50% of human tumors have mutated or non-functional p53. MDM2, a key negative regulator of p53, which is over-expressed in many human tumors, functions by binding to and targeting p53 for proteasomal degradation. Nutlin-3 is a potent inhibitor of p53-MDM2 interaction.[3] (–)-Nutlin-3 is arbitrarily referred to as enantiomer a because it appears as the first peak from chiral purification of racemic nutlin-3 and its absolute stereocenter assignment is not known. It potently inhibits MDM2-p53 binding with an IC_{50} value of 0.09 µM, induces the expression of p53-regulated genes, and exhibits potent antiproliferative activity in cells with functional p53, but not in cells with mutated p53.[3] (–)-Nutlin-3 inhibits the proliferation of exponentially growing human skin and murine fibroblasts with IC_{50} values of 2.2 and 1.3 µM, respectively[3], and induces substantial tumor shrinkage in mice expressing LnCaP, 22Rv1 or MHM cancer cell lines when treated orally with a 200 mg/kg dose twice daily for two weeks.[4]

References

1. El-Deiry, W.S. The p53 pathway and cancer therapy. *Cancer Journal* **11**, 229-236 (1998).
2. Lane, D.P. and Hupp, T.R. Drug discovery and p53. *Drug Discovery Today* **8(8)**, 347-355 (2003).
3. Vassilev, L.T., Vu, B.T., Graves, B., *et al. In vivo* activation of the p53 pathway by small-molecule antagonists of Mdm2. *Science* **303**, 844-848 (2004).
4. Tovar, C., Rosinski, J., Filipovic, Z., *et al.* Small-molecule Mdm2 antagonists reveal aberrant p53 signaling in cancer: Implications for therapy. *Proc. Natl. Acad. Sci. USA* **103(6)**, 1888-1893 (2006).

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