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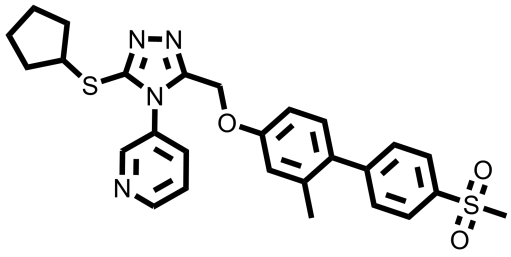
ATPase VCP/p97 Inhibitor – NMS-873

Chemical Name: 3-(3-(cyclopentylthio)-5-(((2-methyl-4'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)oxy)methyl)-4H-1,2,4-triazol-4-yl)pyridine



Molecular Weight:	520.67
Formula:	$C_{27}H_{28}N_4O_3S_2$
Purity:	≥98%
CAS#:	1418013-75-8
Solubility:	DMSO up to 10 mM
Storage	Powder: 4 °C 1 year DMSO: 4 °C 3 months -20 °C 1 year

Biological Activity:

NMS-873 is a potent and specific small molecule allosteric inhibitor of the ATPase VCP/p97 (IC_{50} ~0.03 μM), identified by a high-throughput screening. It is very selective (IC_{50} >10 μM) against all of the AAA ATPases, HSP90 or the 53 kinases tested. Using photo-affinity labeling, structural analysis and mutagenesis, the binding site of NMS-873 was found to be a region spanning the D1 and D2 domains of adjacent protomers encompassing elements important for nucleotide-state sensing and ATP hydrolysis. NMS-873 activated the unfolded protein response, interfered with autophagy, and induced cancer cell death. NMS-873 provided critical validation of VCP as a cancer target, and it raises the possibility that targeting VCP might prevent proteasome inhibitor–resistant tumors from escaping through the aggresome-autophagy pathways and cause them to collapse under the high load of unfolded proteins.

How to Use:

In vitro: NMS-873 was used at 2.5-10 μM final concentration in various in vitro assays.

In vivo: n/a

Reference:

1. Magnaghi P, et al. Covalent and allosteric inhibitors of the ATPase VCP/p97 induce cancer cell death. (2013) Nat Chem Biol. 9(9):548-56