

UNC9630: A chemical handle for FBXO22

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Web link for more details: <https://www.thesgc.org/index.php/chemical-handles/unc9630>

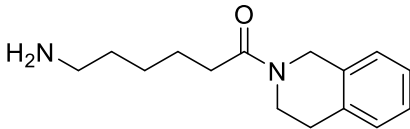
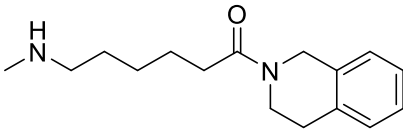
Overview

SGC in collaboration with Lindsey James' lab at the University of North Carolina at Chapel Hill (UNC) has developed a chemical handle for FBXO22, UNC9630. The handle is an amine pro-drug.

Summary

Chemical handle name	UNC9630
Negative control compound	UNC9631
Target(s) (synonyms)	FBXO22 (FBX22)
Recommended <i>in vitro</i> assay concentration	N/A
Suitability for <i>in vivo</i> use and recommended dose	Handles are not for <i>in vivo</i> use
Publications	https://doi.org/10.1038/s41589-024-01660-y , https://doi.org/10.1021/jacs.3c01421
Related chemical probe degrader	UNC8732
<i>In vitro</i> assay(s) used to characterise	Thermal stability
Cellular assay(s) for target-engagement	In cell western
ChemicalProbes.org	

Chemical Handle Structure and Use

<p>UNC9630</p> 	<p>UNC9631</p> 
SMILES: <chem>O=C(CCCCCN)N1CC2=CC=CC=C2CC1</chem>	SMILES: <chem>O=C(CCCCCNC)N1CC2=CC=CC=C2CC1</chem>
InChiKey: WTLPOIOETUIQS-UHFFFAOYSA-N	InChiKey: ISHLVDCNCOPCY-UHFFFAOYSA-N
Molecular weight: 246.4	Molecular weight: 260.4
<p>Storage: As a dry powder or as DMSO stock solutions (10 mM) at -20 °C. DMSO stocks beyond 3-6 months or 2 freeze/thaw cycles should be tested for activity before use Dissolution: Soluble in DMSO up to 50 mM; use only 1 freeze/thaw cycle per aliquot</p>	

Chemical Handle Profile

***In vitro* Potency & Selectivity:** UNC9630 is an amine prodrug. To demonstrate binding in cell free conditions, a surrogate bisulfite prodrug UNC10089 was used. UNC10089 stabilizes SKP1/FBXO22 (complex) and FBXO22's FIST_C domain in a dose-dependent manner; 100 μM of UNC10089 stabilizes SKP1/FBXO22 by 4 °C, and the FIST_C domain by 4.8 °C.

Potency in Cells and Cellular Target Engagement: An in-cell western shows that UNC9630 competes with UNC8732 (an NSD2 degrader that employs the UNC9630 handle) for binding to FBXO22, and blocks NSD2 degradation. FBXO22 knockdown abolishes UNC8732 mediated degradation.