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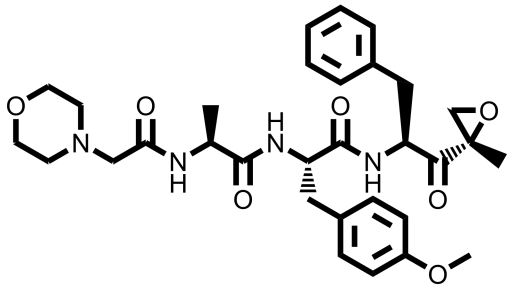
Immunoproteasome Inhibitor – ONX-0914 (PR-957)

Chemical Name: (S)-3-(4-methoxyphenyl)-N-((S)-1-((S)-2-methyloxiran-2-yl)-1-oxo-3-phenylpropan-2-yl)-2-((S)-2-(2-morpholinoacetamido)propanamido)propanamide



Molecular Weight:	580.67
Formula:	$C_{31}H_{40}N_4O_7$
Purity:	≥98%
CAS#:	960374-59-8
Solubility:	DMSO up to 100 mM
Storage	Powder: 4 °C 1 year DMSO: 4 °C 3 month -20 °C 1 year

Biological Activity:

ONX-0914 is an immunoproteasome inhibitor. It selectively inhibits low–molecular mass polypeptide-7 (LMP7, encoded by Psmb8), the chymotrypsin-like subunit of the immunoproteasome, with an IC_{50} < 100 nM. It blocked presentation of LMP7-specific, MHC-I–restricted antigens in vitro and in vivo with minimal cross-reactivity for the constitutive proteasome. Selective inhibition of LMP7 by ONX-0914 blocked production of interleukin-23 (IL-23) by activated monocytes and interferon-gamma and IL-2 by T cells. In mouse models of rheumatoid arthritis and lupus, ONX-0914 treatment reversed signs of disease and resulted in reductions in cellular infiltration, cytokine production and autoantibody levels at well-tolerated doses. ONX 0914 is a good chemical probe to reveal a unique role for LMP7 in controlling pathogenic immune responses and provide a therapeutic rationale for autoimmune disorders, such as rheumatoid arthritis, inflammatory bowel disease and lupus.

How to Use:

In vitro: ONX-0914 was used at 0.1-0.3 μM in vitro and in cellular assays.

In vivo: ONX-0914 was dosed to mice by either intravenous or subcutaneous administration at 2-10 mg/kg once a day for 5 days.

Reference:

1. Muchamuel T, et al. A selective inhibitor of the immunoproteasome subunit LMP7 blocks cytokine production and attenuates progression of experimental arthritis. (2009) Nat Med. 15(7):781-7.
2. Basler M, et al. Prevention of experimental colitis by a selective inhibitor of the immunoproteasome. (2010) J Immunol. 185(1):634-41.
3. Huber EM, et al. Immuno- and constitutive proteasome crystal structures reveal differences in substrate and inhibitor specificity. (2012) Cell. 148(4):727-38.
4. Kalim KW, et al. Immunoproteasome subunit LMP7 deficiency and inhibition suppresses Th1 and Th17 but enhances regulatory T cell differentiation. (2012) J Immunol. 189(8):4182-93.