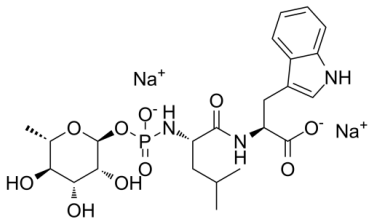
Data Sheet

Product Name:	Phosphoramidon (Disodium)
Cat. No.:	CS-6924
CAS No.:	164204-38-0
Molecular Formula:	C23H32N3Na2O10P
Molecular Weight:	587.47
Target:	Angiotensin-converting Enzyme (ACE); Neprilysin
Pathway:	Metabolic Enzyme/Protease
Solubility:	H2O : ≥ 140 mg/mL (238.31 mM)



BIOLOGICAL ACTIVITY:

Phosphoramidon Disodium is a **metalloprotease** inhibitor. Phosphoramidon inhibits endothelin-converting enzyme (**ECE**), neutral endopeptidase (**NEP**), and angiotensin-converting enzyme (**ACE**) with **IC_{50}** values of 3.5, 0.034, and 78 μM, respectively. IC50 & Target: IC50: 3.5 μM (ECE), 34 nM (NEP), 78 μM (ACE)[1] **In Vitro:** Phosphoramidon is a naturally occurring glycopeptide first isolated from a strain of Streptomyces tanashiensis. It has a unique chemical structure featuring a phosphoramidate linkage between a-L-rhamnose and L-leucineL-tryptophan. As a microbial metabolite, phosphoramidon exhibits potent inhibitory activity against thermolysin, a zinc endopeptidase isolated from Bacillus thermoproteolyticus (K_i=32 nM)[2]. **In Vivo:** Intranasal administration of phosphoramidon produces significantly elevated cerebral Aβ levels in wild-type mice. Furthermore, intranasal phosphoramidon administration in double knockout mice lacking NEP and NEP2 also shows increased levels of Aβ40[3]. Phosphoramidon blocks the formation of endothelin-1 (ET-1), a proinflammatory mediator implicated in the pathogenesis of a variety of lung diseases. Phosphoramidon significantly reduces LPS-induced pulmonary inflammation as measured by lung histology, neutrophil content of bronchoalveolar lavage (BAL) fluid, percent tumor necrosis factor receptor 1 (TNFR1)-labeled BAL macrophages, and alveolar septal cell apoptosis[4]. Phosphoramidon significantly decreased ET-1 levels, causing a concomitant big ET-1 increase and dose-dependently attenuated indomethacin-induced gastric mucosal damage[5].

PROTOCOL (Extracted from published papers and Only for reference)

Kinase Assay: [2]The K_i values are determined in a 50 mM Tris-HCl, 10 mM $CaCl_2$ buffer (pH 7.5) with FA-Gly-Leu-NH2 (FAGLA) as a substrate by using an Agilent 8453 UV-vis spectrophotometer in triplicate. Henderson plots are employed for the calculation of K_i values. A mixture of buffer (970 μL), phosphoramidon (0-80 nM, 20 μL), and thermolysin (40 nM, 10 μL) is incubated at 25 C for 15 min in a cuvette (2 mL). A solution of FAGLA (0.1-0.5 mM, 1.0 mL) in Tris buffer pH 7.5 is added into the cuvette. The absorbance decrease upon cleavage of FAGLA by thermolysinis recorded at 340 nm wavelength for 5 min. The concentration of thermolysinis determined from the molar extinction coefficient[2].

Animal Administration: [3][4]Mice[3]

Phosphoramidon is dissolved in phosphate-buffered saline (PBS+1 mM ascorbic acid) at a concentration of 30 mM. Anesthetized mice are placed on their backs and eight 3-μL drops of phosphoramidon solution are administered to alternating nares every 2 min. This is done once per day for 5 days. Mice are euthanized under anesthesia for tissue collection 2 h post phosphoramidon administration on day 5. Control mice are treated with intranasal PBS vehicle solution alone. Brains are removed and dissected into the desired brain regions before being homogenized in 5 M guanidine HCl to extract total Aβ. After centrifugation (16,000×g), the supernatants are diluted tenfold and Aβ (1-42 and 1-40) is quantified by specific ELISA.

Rats[4]

Animals are treated with phosphoramidon either intraperitoneally or intratracheally via nebulization. To examine the effects of intraperitoneal administration, animals are injected with 0.5 mg of phosphoramidon dissolved in 0.5 mL of phosphatebuffered saline

(PBS). For the nebulization studies, animals are placed in an exposure chamber and treated for 1 hour with an aerosol composed of a 0.1% solution of phosphoramidon dissolved in distilled water. The aerosolized phosphoramidonis delivered through a ceiling port via a Misty-Ox nebulizer attached to an air compressor. Negative pressure is applied by a blower attached to a secondary outflow port to insure proper circulation of the aerosol.

References:

[1]. Kukkola PJ, et al. Differential structure-activity relationships of phosphoramidon analogues for inhibition of three metalloproteases: endothelin-converting enzyme, neutral endopeptidase, and angiotensin-converting enzyme.J CardiovascPharmacol. 1995;26Suppl 3:S65-8.

[2]. Sun Q, et al. Synthesis and enzymatic evaluation of phosphoramidon and its β anomer: Anomerization of α-l-rhamnose triacetate upon phosphitylation.Bioorg Med Chem. 2013 Nov 1;21(21):6778-87.

[3]. Hanson LR, et al. Intranasal phosphoramidon increases beta-amyloid levels in wild-type and NEP/NEP2-deficient mice.J MolNeurosci. 2011 Mar;43(3):424-7.

[4]. Bhavsar TM, et al. Phosphoramidon, an endothelin-converting enzyme inhibitor, attenuates lipopolysaccharide-induced acute lung injury.Exp Lung Res. 2008 Mar;34(3):141-54.

[5]. Matsumaru K, et al. Phosphoramidon, an inhibitor of endothelin-converting enzyme, prevents indomethacin-induced gastric mucosal damage in rats.Life Sci. 1998;62(7):PL79-84.

CAIndexNames:

L-Tryptophan, N-[N-[[(6-deoxy-α-L-mannopyranosyl)oxy]hydroxyphosphinyl]-L-leucyl]-, sodium salt (1:2)

SMILES:

O=C([O-])[C@H](CC1=CNC2=CC=CC=C12)NC([C@H](CC(C)C)NP([O-])(O[C@H]3[C@@H]([C@@H]([C@H]([C@H](C)O3)O)O)O)=O)=O.[Na+].[Na+]

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