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Val-boroPro - CAS 150080-09-4 - Calbiochem An orally available, potent, reversible, and transition state analog inhibitor of DPP-IV (IC?? = 26 nM)

Art. ID SAF-5314650001

Unit EA

Description

A prolineboronic acid-based broad-spectrum DDP IV activity and/or structural homologue (DASH) family dipeptidyl peptidases inhibitor that converts in solution between the protonated active form and a cyclized inactive form due to a reversible intramolecular B-N dative bond formation of the non-protonated Val-boroPro (kinact = 6.4 x 10--4 s- and kcyc = 6.4 x 10-5 s- at pH 7.8). Although equilibrium favors cyclization at basic pH, high affinity binding (kon & koff toward CD26 at pH 7.8 = 5.02 x 106 M-s- and 77.8 x 10-6 s-, respectively) drives the equilibrium away from cyclization and traps the active form in enzyme-bound state with prolonged incubation. Reported to inhibit DPP7/DPPII/QPP (IC50/[Substrate]/rxn time at pH 5.5 = 15 nM/500 &#181,M Lys-Pro-MNA/1 h & 310 nM/50 &#181,M Nle-Pro-AMC/15 min), CD26/DPPIV (IC50 = 26 nM, 500 &#181,M Ala-Pro-MNA for 1 h at pH 7.8), fibroblast activation protein/FAP (IC50 = 40 nM, 250 &#181,M Ala-Pro-AFC at pH 2.0), DPP8 (IC50 = 4 nM, 100 &#181,M Ala-Pro-AFC for 15 min at pH 8.0), DDP9 (IC50 = 11 nM, 100 &#181,M Gly-Pro-AMC for 30 min at pH 7.4) with little potency against 9 other proteases (IC50 >100 &#181,M, aminopeptidase P, chymoptrypsin, leukocyte elastase, plasma kallikrein, plasmin, prolidase, thrombin, trypsin, tryptase), while contradictory reports regarding prolyl endopeptidase/PEP/PREP inhibition exist (e.g. IC50 = 390 nM/50 &#181,M Z-Gly-Pro-AMC/pH 7.5/30 min vs. 25 &#181,M/500 &#181,M Z-Gly-Pro-MNA/pH 7.8/60 min). Shown to promote the propagation of human BM CD34+ cells by stimulating stromal cells cytokine production in vitro (min EC 0.1 nM) and display hematopoietic stimulatory effect in mice in vivo (min ED 2 &#181,g/mouse/12 h, p.o.). Although orally available in mice and rats, caution must be taken not to exceed toxicity levels (MTD = 25 &#181,g/mL using Sprague-Dawley rats, LD50 ~0.5 mg/mL in 24 survival test using Fisher rats, p.o.) for in vivo studies., An orally available amino boronic acid dipeptide with antihyperglycemic and anticancer properties. Acts as a highly potent, reversible, and transition state analog inhibitor of dipeptidyl peptidase IV (DPP-IV, IC50 = 26 nM, Ki = 180 pM). Also inhibits the activity of other prolyl peptidases (IC50 = 15 nM for DPP-II, and Ki = 1.5 nM and 760 pM for DPP8 and DPP9, respectively) and at much higher concentrations affects the activities of quiescent cell proline dipeptidase (QPP, DPP7, IC50 = 310 nM), PEP (IC50 = 390 nM) and fibroblast activation protein (FAP, IC50 = 560 nM). However, it does not inhibit the activity of trypsin, chymoptrypsin, thrombin, plasmin, tryptase, leukocyte elastase, and plasma kallikrein even at high levels (~100 &#181,M). Promotes hematopoiesis and the growth of primitive hematopoietic progenitor cells by increasing the production of G-CSF, IL-6, and IL-11 by bone marrow stromal cells in mice. Although it has no direct cytotoxic effect on tumors in vitro, but oral administration in mice is shown to reduce the growth of syngeneic tumors derived from fibrosarcoma (WEHI164), lymphoma (EL4 and A20/2J), melanoma (B16-F10), and mastocytoma (P815) cell lines and augments antibody-dependent cell-mediated cytotoxicity. Note: In aqueous physiological solutions, it can cyclize in a time-dependent manner causing a 100-fold diminution in its inhibitory potency. However, at lower pH range it remains in an active open chain form. Maximum tolerated dose in mice or rats is ~ 25 &#181,g/kg.Please note that the molecular weight for this compound is batch-specific due to variable water content.

Text/Information	Analyte/Parameter	CAS number	Concentration/Value	Unit	Method	Source
	Talabostat Mesylate	[150080-09-4]				