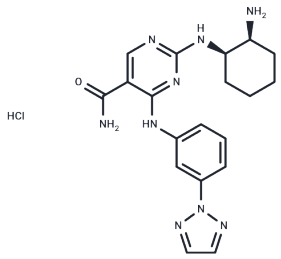
Data Sheet (Cat.No.T2696)

TargetMol

PRT062607 hydrochloride

Chemical Properties



CAS No. : 1370261-97-4

Formula: C19H23N9O·HCl

Molecular Weight: 429.91

Storage: Powder: -20°C for 3 years | In solvent: -80°C for 1 year
Actual storage temperature shall be subject to the COA.

Biological Description

Description	PRT062607 hydrochloride (P505-15 Hydrochloride) is a selective inhibitor of Syk (IC50: 1 nM). It displays at least 80-fold selectivity for Syk over other kinases.
Targets(IC50)	Apoptosis,MLK,FAK,PYK2,Syk,PAK,Src
In vitro	PRT062607 (P505-15) is a highly specific and potent inhibitor of purified Syk (IC50 1-2 nM). In human whole blood, P505-15 potently inhibited B cell antigen receptor-mediated B cell signaling and activation (IC50 0.27 and 0.28 μM, respectively) and Fcε receptor 1-mediated basophil degranulation (IC50 0.15 μM). Similar levels of ex vivo inhibition were measured after dosing in mice (Syk signaling IC50 0.32 μM) [1]. P505-15 abrogated the pro-survival effect of anti-IgM and induced CLL cell apoptosis. Treatment with P505-15 (2 mM/mL) decreased CLL cell viability to 62.9 ± 5.1% after 48 hours. Treatment with lower concentrations of PRT318 and P505-15 also reduced the viability of CLL cells [2].
In vivo	Demonstrating a rapid onset of action, 0.5 h after oral administration of 30 mg/kg P505-15, Syk activity was reduced by 80% and nearly completely suppressed for the next 5 h relative to vehicle control-treated mice. Syk activity remained more than 60% suppressed for the first 8 h postdosing, returning to levels of vehicle control treatment by 24 h. At the lower dose of 15 mg/kg, more than 50% suppression of Syk activity was observed between 2 and 6 h after oral administration of the compound [1].
Kinase Assay	Potency of Syk inhibition was determined by using a fluorescence resonance energy transfer (FRET) assay. The extent of substrate phosphorylation by Syk was measured in the presence of various P505-15 concentrations. Syk activity was determined by a fluorescent antibody specific for phosphorylated tyrosine by using the increase of FRET. Twelve concentrations were tested for dose response. Specificity and potency of kinase inhibition was determined by evaluation of P505-15 in the Millipore KinaseProfiler panel of 270 independent purified kinase assays. For profiling, P505-15 was tested in duplicate at two concentrations at a fixed concentration of ATP. Subsequently, IC50 determinations using the radioactive assays were carried out at an ATP concentration optimized for each individual kinase. All radioactive ATP incorporation enzyme assays were performed at Millipore UK [1].
Cell Research	NLC co-cultures were established by suspending PBMC from patients with CLL in complete RPMI medium with 10% fetal bovine serum and penicillin-streptomycin-glutamine to a concentration of 107 cells/mL (total 2 mL). Cells were incubated for 14

Cell Research	days in 24-well plates as previously described. To evaluate whether the Syk inhibitors PRT318 and P505-15 could overcome the protective effect of NLC, CLL cells were cultured under standardized conditions on NLC or in suspension, in the presence or absence of PRT318 and P505-15. At the indicated time points, CLL cells were collected and assayed for cell viability as previously described [2].
Animal Research	All animal studies were performed in strict accordance with the Institutional Animal Care and Use Committee ethical guidelines. Female BALB/c mice received a single oral dose of 15 or 30 mg/kg P505-15 and were anesthetized with a subcutaneous ketamine cocktail, and blood was harvested via cardiac puncture at 0.5, 1, 2, 3, 4, 5, 6, 8, and 24 h postdose, (n = 3/time point; n = 8 vehicle controls). Blood was dispensed into three heparin-containing tubes, one for determination of drug concentration and the remaining two for ex vivo stimulation with isotype control or anti-mouse IgD antibody for 10 min. Blood was processed for intracellular phospho-flow cytometry to evaluate BCR signaling as described earlier; mouse B cells were detected by using CD45R-B220 PerCP-conjugated antibody. Plasma samples were analyzed for P505-15 concentration by using a liquid chromatography tandem mass spectrometer. The analytical range was 2 to 5000 ng/ml [1].

Solubility Information

Solubility	Ethanol: < 1 mg/mL (insoluble or slightly soluble), H2O: 79 mg/mL (183.76 mM),Sonication is recommended. DMSO: 250 mg/mL (581.52 mM),Sonication is recommended. (< 1 mg/ml refers to the product slightly soluble or insoluble)
In vivo Formulation	10% DMSO+40% PEG300+5% Tween 80+45% Saline: 2 mg/mL (4.65 mM),Sonication is recommended. *Please add the solvents sequentially, clarifying the solution as much as possible before adding the next one. Dissolve by heating and/or sonication if necessary. Working solution is recommended to be prepared and used immediately. The formulation provided above is for reference purposes only. In vivo formulations may vary and should be modified based on specific experimental conditions.*

Preparing Stock Solutions

	1mg	5mg	10mg
1 mM	2.3261 mL	11.6303 mL	23.2607 mL
5 mM	0.4652 mL	2.3261 mL	4.6521 mL
10 mM	0.2326 mL	1.163 mL	2.3261 mL
50 mM	0.0465 mL	0.2326 mL	0.4652 mL

Please select the appropriate solvent to prepare the stock solution, according to the solubility of the product in different solvents. Please use it as soon as possible.

Note: The dilution table applies only to solid products. For liquid products, please calculate the stock solution based on the stated concentration and/or density.

Reference

Coffey G, et al. Specific inhibition of spleen tyrosine kinase suppresses leukocyte immune function and inflammation in animal models of rheumatoid arthritis. J Pharmacol Exp Ther. 2012 Feb;340(2):350-9.
Hoellenriegel J, et al. Selective, novel spleen tyrosine kinase (Syk) inhibitors suppress chronic lymphocytic leukemia B-cell activation and migration. Leukemia. 2012 Jul;26(7):1576-83.

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